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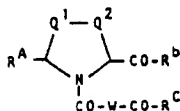
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54 Thiazolidine and pyrrolidine compounds, processes for their preparation and pharmaceutical compositions containing them.

57 Thiazolidine and pyrrolidine compounds which have the general formula



and salts thereof for preventing or relieving diabetic complications and for reducing blood pressure, the processes for their preparation, and the compositions comprising them and pharmaceutically acceptable excipient(s).

- 1 lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

5

$R^b$  is selected from the group consisting of

- (a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and  
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and  
10 (iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;
- (b) (i) phenyl and naphthyl, and  
15 (ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-  
20 sulfonyl and lower alkylsulfinyl;
- (c) (i) furyl, thienyl and pyridyl, and  
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen,  
25 nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

1 -O-, -CO-, -S-, -SO-, -SO<sub>2</sub>-,  $\begin{array}{c} \text{--C--} \\ \parallel \\ \text{N--R}^{20} \end{array}$ , -NHCONH-,  $\begin{array}{c} \text{--N--} \\ \diagup \quad \diagdown \\ \text{N} \end{array}$  or  $\begin{array}{c} \text{--N--} \\ | \\ \text{R}^{21} \end{array}$  ;

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;  
 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>,  
 R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> each is R<sup>d</sup>;

5 R<sup>a</sup> is R<sup>b</sup> when W is  $\begin{array}{c} \text{R}^{23} \\ | \\ \text{--CH--NH--C--} \\ | \quad | \quad | \\ \text{R}^{22} \quad \text{R}^{24} \end{array}$  or  $\begin{array}{c} \text{--CH--(CH)}_{0-2} \\ | \quad | \\ \text{R}^{25} \quad \text{R}^{26} \end{array}$ , wherein  
 R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup> and R<sup>26</sup> each is R<sup>d</sup>;

R<sup>a</sup> is selected from the group consisting of

(i) hydrogen, lower alkyl and lower alkenyl, and

0 (ii) lower alkyl and lower alkenyl substituted by at least  
 one substituent selected from the group consisting of  
 lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-  
 lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower  
 alkylamino, dialkylamino, acylamino, mercapto, acylmercapto,  
 lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-  
 carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-  
 5 sulfcnyl and lower alkylsulfinyl;

R<sup>b</sup> is selected from the group consisting of

(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and

(ii) aralkyl, heteroalkyl, aralkenyl and heteroaralkenyl  
 substituted by at least one substituent selected from the  
 group consisting of lower alkyl, lower alkenyl, halogeno-  
 0 lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,  
 acyloxy, halogen, nitro, cyano, amino, lower alkylamino,  
 dialkylamino, acylamino, mercapto acylmercapto, lower  
 alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-  
 carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-  
 sulfonyl and lower alkylsulfinyl, and

5 (iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,

- 1 selected from the group consisting of lower alkyl, lower alkoxy,  
lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro,  
cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl,  
halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl,  
sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl  
5 (c) (i) furyl, thienyl and pyridyl, and  
(ii) furyl, thienyl and pyridyl substituted by at least one  
substituent selected from the group consisting of lower alkyl,  
lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,  
halogen, nitro, cyano, acylamino, mercapto, acylmercapto,  
halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-  
dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-  
10 aminosulfonyl and lower alkylsulfinyl;  
and salts thereof.

2. A compound of claim 1 wherein  $-Q^1-Q^2-$  is  $-CH_2CH_2-$ ,  
 $-SCH_2-$  or  $-CH_2S-$ .

- 15 3. A compound of claim 1 wherein  $R^a$  is hydrogen, methyl,  
ethyl, 1-methylethyl, propyl, 2-methylpropyl, butyl, 2,6-  
dimethyl-5-heptenyl, cyclohexyl, S-acetyl-2-mercaptoethyl or  
2-mercaptoethyl.

- 20 4. A compound of claim 1 wherein  $R^b$  is benzyl, 2-phenyl-  
ethyl, 4-methylbenzyl, 4-methoxybenzyl, 2-hydroxybenzyl, 4-  
hydroxybenzyl, 3-fluorobenzyl, 3-nitrobenzyl, 3-cyanobenzyl,  
2-(4-methoxyphenyl)ethyl, 2-(2-hydroxyphenyl)ethyl, 2-(4-  
hydroxyphenyl)ethyl, 2-(3-fluorophenyl)ethyl, 2-[3-(trifluoro-  
methyl)phenyl]ethyl, 2-(3-nitrophenyl)ethyl, 2-(3-cyanophenyl)-  
ethyl, 2-pyridylmethyl, 4-pyridylmethyl, 2-furylmethyl, 2-(2-  
pyridyl)ethyl, 2-(4-pyridyl)ethyl, 2-(2-furyl)ethyl, phenyl,  
25 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl,  
2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl,  
3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethyl-

1            $R^d$  is selected from the group consisting of  
(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-  
aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,  
carboxy, amino, mercapto and sulfo, and  
(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,  
5       alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy,  
amino, mercapto and sulfo substituted by at least one substituent  
selected from the group consisting of lower alkyl, lower alkenyl,  
lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl,  
hydroxy, carboxy, amino, guanidino, mercapto, acylamino,  
acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro,  
cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio  
10       and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and  
(ii) phenyl and naphthyl substituted by at least one substituent  
selected from the group consisting of lower alkyl, lower alkoxy,  
lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen,  
nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-  
15       lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower  
alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl  
and lower alkylsulfinyl;

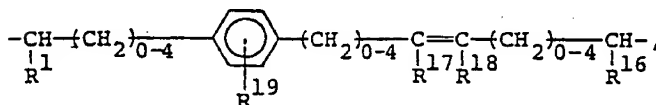
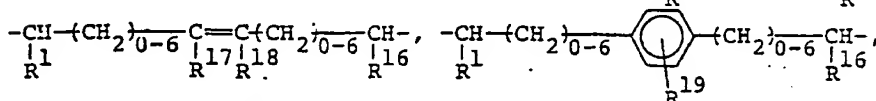
(c)(i) furyl, thienyl and pyridyl, and  
(ii) furyl, thienyl and pyridyl substituted by at least one  
substituent selected from the group consisting of lower alkyl,  
lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,  
20       halogen, nitro, cyano, acylamino, mercapto, acylmercapto,  
halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-  
dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-  
aminosulfonyl and lower alkylsulfinyl;

and salts thereof which are useful as agents for therapy or  
25       prophylaxis of the diabetic complication because they inhibit  
strongly aldose reductase, and as antihypertensive agents  
because they inhibit angiotensin I-converting enzyme.

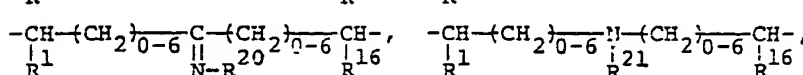
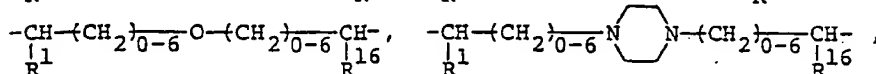
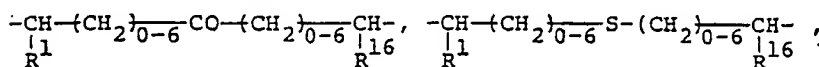
- 1 dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-5-sulfamoylphenyl, 3-(methylsulfinyl)phenyl, 3-(difluoromethoxy)phenyl, 2-furyl, 2-(5-methyl)furyl, 2-thienyl, 3-pyridyl or 4-pyridyl.

5

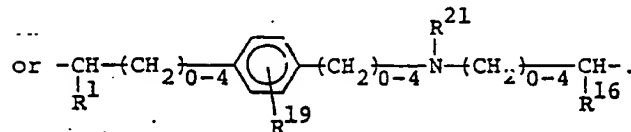
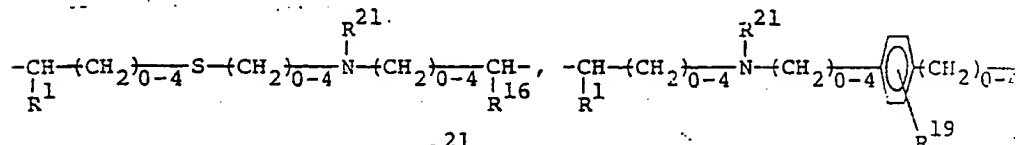
7. A compound of claim 1 wherein W is  $-\text{CH}(\text{R}^1)-(\text{CH}_2)_{0-12}-\text{CH}(\text{R}^{16})-$



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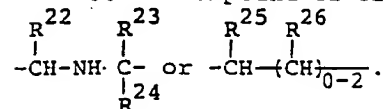


5



10

8. A compound of claim 1, wherein  $\text{R}^A$  is  $\text{R}^B$  when W is



25

9. A compound of claim 4 which is (4R)-3-[8-(ethoxycarbonyl)octanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid.

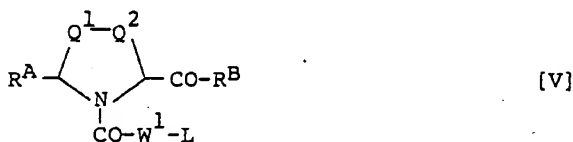
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- 1 (ii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of [IV] (e.g., above-mentioned)

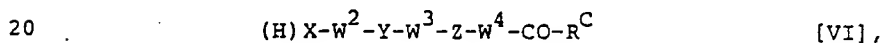


wherein  $\text{W}^1$  is  $\begin{bmatrix} \text{R}^1 \\ | \\ \text{C} \\ | \\ \text{R}^2 \end{bmatrix} \begin{bmatrix} \text{R}^3 \\ | \\ \text{C} \\ | \\ \text{R}^4 \end{bmatrix}_m$ , and may be protected such as (i)

- 10 above, L is a leaving group (e.g., halogen, alkylsulfonyl, arylsulfonyl, etc.), by the same methods as described in (i) above to produce a compound of the formula [V]



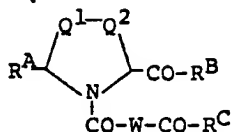
and then reaction of a compound of the formula [V] with a compound of the formula [VI]



wherein  $\text{W}^2$  is  $\begin{bmatrix} \text{R}^5 \\ | \\ \text{C} \\ | \\ \text{R}^6 \end{bmatrix} \begin{bmatrix} \text{R}^7 \\ | \\ \text{C} \\ | \\ \text{R}^8 \end{bmatrix}_n$ ,  $\text{W}^3$  is  $\begin{bmatrix} \text{R}^9 \\ | \\ \text{C} \\ | \\ \text{R}^{10} \end{bmatrix} \begin{bmatrix} \text{R}^{11} \\ | \\ \text{C} \\ | \\ \text{R}^{12} \end{bmatrix}_q$ ,  $\text{W}^4$  is

25  $\begin{bmatrix} \text{R}^{13} \\ | \\ \text{C} \\ | \\ \text{R}^{14} \end{bmatrix} \begin{bmatrix} \text{R}^{15} \\ | \\ \text{C} \\ | \\ \text{R}^{16} \end{bmatrix}_s$ , and  $\text{W}^2$ ,  $\text{W}^3$ ,  $\text{W}^4$ , X, Y, Z and  $\text{R}^C$  may be

1 16. A process for preparing a compound of the formula [I]



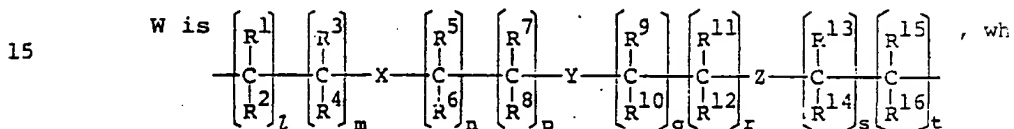
[I]

wherein

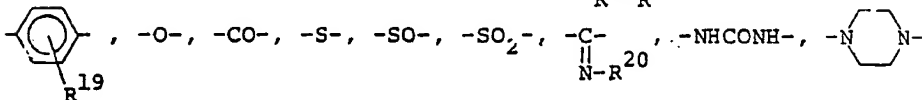
10  $\text{Q}^1$  and  $\text{Q}^2$  each is methylene or sulfur, but  $\text{Q}^1$  and  $\text{Q}^2$  are not sulfur at the same time;

$\text{R}^{\text{A}}$  is  $\text{R}^{\text{a}}$  or  $\text{R}^{\text{b}}$ ;

$\text{R}^{\text{B}}$  and  $\text{R}^{\text{C}}$  each is  $\text{R}^{\text{C}}$ ;



X, Y and Z each is single bond,  $-\text{CH}_2-$ ,  $-\text{C}=\text{C}-$ ,  $-\text{C}\equiv\text{C}-$ ,  
 $\text{R}^{17} \quad \text{R}^{18}$



20 or  $-\text{N}-$ ;  
 $\text{R}^{21}$

$l, m, n, p, q, r, s$  and  $t$  each is 0, 1, 2 or 3;

$\text{R}^1, \text{R}^2, \text{R}^3, \dots, \text{R}^{20}$  and  $\text{R}^{21}$  each is  $\text{R}^{\text{d}}$ ;

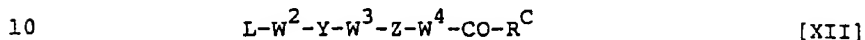
25  $\text{R}^{\text{A}}$  is  $\text{R}^{\text{b}}$  when W is  $-\text{CH}-\text{NH}-\text{C}-$  or  $-\text{CH}-\text{CH}-$ , wherein  $\text{R}^{22}$ ,  
 $\text{R}^{23}$   $\text{R}^{24}$   $\text{R}^{25}$   $\text{R}^{26}$   
 $\text{R}^{23}, \text{R}^{24}, \text{R}^{25}$  and  $\text{R}^{26}$  each is  $\text{R}^{\text{d}}$ .

9

- 1 (v) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid [XI] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, lactone, thiolactone, etc.)



and then with a compound of the formula [XII]

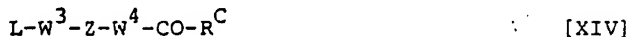


by the same method as (ii) above.

- (vi) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII] (e.g.,  
15 mentioned in (v) above)



- 20 and then with a compound of the formula [XIV]



by the same method as (ii) above.

- 25 (vii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the

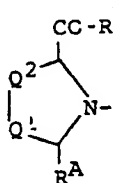
- 1 lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy,  
 halogeno-lower alkoxy aralkyloxy, aryloxy, acyloxy, halogen, nitr  
 cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto  
 acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl,  
 aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkyl-  
 5 aminosulfonyl and lower alkylsulfinyl;

$R^C$  is selected from the group consisting of

- (a) (i) hydroxy, lower alkoxy and amino, and  
 (ii) lower alkoxy and amino substituted by at least one substitue  
 selected from the group consisting of lower alkyl, aralkyl,  
 heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy,  
 10 aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy,  
 aryl, heteroaryl, substituted aralkyl and substituted aryl  
 wherein the substituent is lower alkyl, lower alkoxy, halogen  
 or amino;

- (b) (i) aryloxy and heteroaryloxy, and  
 (ii) aryloxy and heteroaryloxy substituted by at least one  
 15 substituent selected from the group consisting of lower alkyl,  
 hydroxy, lower alkoxy, halogen and amino, and

(c)



20  $R^d$  is selected from the group consisting of

- (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-  
 aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,  
 carboxy, amino, mercapto and sulfo, and  
 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,  
 alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy,  
 25 amino, mercapto and sulfo substituted by at least one  
 substituent selected from the group consisting of lower alkyl,  
 lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl,  
 acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto,

1 have presented that cataract is caused by the accumulation  
of sugar alcohols [Exptl. Eye. Res., 6, 1 (1967)]. A report  
of Kinoshita et al. has demonstrated that aldose reductase  
which reduced aldose to the corresponding sugar alcohols  
5 was involved in the initiation of these diabetic  
complications and that effective inhibitors of aldose  
reductase were useful [Jpn. J. Ophthalmol., 20, 339 (1976)].  
On the basis of the above information, aldose reductase  
inhibition of the compounds [I] of this invention was tested.  
10 The results of the examinations demonstrated that these  
compounds have potent inhibitory activities on aldose  
reductase, and therefore they are useful as drugs for therapy  
or prophylaxis of the diabetic complications.

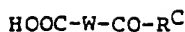
On the other hand, it has been known that a kind of the  
15 derivatives of thiazolidine- or pyrrolidinecarboxylic acid  
have potent inhibitory activity to angiotensin I-converting  
enzyme, but thiazolidine and pyrrolidine compounds of this  
invention are novel compounds, and have more potent inhibitory  
activities to angiotensin I-converting enzyme. Furthermore,  
20 the compounds of this invention are prepared by convenient  
methods, and are superior to the stability.

Thus, the compounds of this invention are useful as  
therapeutic or prophylactic agents and antihypertensive  
agents.

25

The compound of formula [I] can form the conventional

1

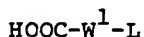


[III]

wherein  $\text{R}^{\text{C}}$  and W may include suitable protection of any reactive groups, followed by removal of protective groups, if necessary to yield a compound of the formula [I];

5

(ii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IV]

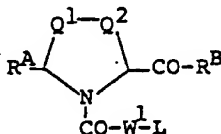


[IV]

10

wherein  $\text{W}^1$  is  $\begin{bmatrix} \text{R}^1 \\ | \\ \text{---C---} \\ | \\ \text{R}^2 \end{bmatrix} \text{L} \begin{bmatrix} \text{R}^3 \\ | \\ \text{---C---} \\ | \\ \text{R}^4 \end{bmatrix}$ , and may include suitable protection of any reactive groups, and L is a leaving group to yield a compound of the formula [V]

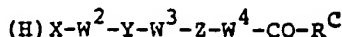
15



[V],

20

and then reacting a compound of the formula [V] with a compound of the formula [VI]



[VI]

25

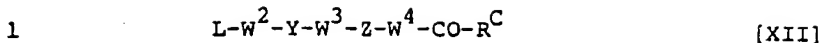
wherein  $\text{W}^2$  is  $\begin{bmatrix} \text{R}^5 \\ | \\ \text{---C---} \\ | \\ \text{R}^6 \end{bmatrix} \begin{bmatrix} \text{R}^7 \\ | \\ \text{---C---} \\ | \\ \text{R}^8 \end{bmatrix}$ ,  $\text{W}^3$  is  $\begin{bmatrix} \text{R}^9 \\ | \\ \text{---C---} \\ | \\ \text{R}^{10} \end{bmatrix} \begin{bmatrix} \text{R}^{11} \\ | \\ \text{---C---} \\ | \\ \text{R}^{12} \end{bmatrix}$ ,  $\text{W}^4$  is  $\begin{bmatrix} \text{R}^{13} \\ | \\ \text{---C---} \\ | \\ \text{R}^{14} \end{bmatrix} \begin{bmatrix} \text{R}^{15} \\ | \\ \text{---C---} \\ | \\ \text{R}^{16} \end{bmatrix}$  and  $\text{W}^2$ ,  $\text{W}^3$ ,  $\text{W}^4$ , X, Y, Z and  $\text{R}^{\text{C}}$  may include suitable protection

13  
EXAMPLE 1

(4R)-3-(7-Carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 20)

5 (4R)-2-(2-Hydroxyphenyl)-4-thiazolidinecarboxylic acid (6.8g,) in N sodium hydroxide (30ml) and octanedioyl dichloride (6.3g,) were added dropwise to 1M potassium carbonate (60ml) with stirring under ice-cooling. After the addition, the reaction mixture was stirred for 1 hour at the same temperature and for additional 1 hour at room temperature. The solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil<sup>\*2</sup> was purified by silica gel column chromatography to give 7.0g (61%) of the titled compound: mp 155-157°C (dec.) (ethyl acetate);  $[\alpha]_D^{27} +134.1^\circ$  (c=0.5, methanol). IR (nujol,  $\text{cm}^{-1}$ ): 3220 (OH), 1710 (COOH), 1620 (CON), 1600 (aromatic), 1415, 1235, 1172, 950, 760. NMR (DMSO- $d_6$ ,  $\delta$ ): 0.53-1.73 (8H, m,  $-\text{CH}_2(\text{CH}_2)_4-\text{CH}_2-$ ), 1.77-2.57 (4H, m,  $-\text{CH}_2(\text{CH}_2)_4-\text{CH}_2-$ ), 3.03 (1H, AB<sub>Q</sub> (A part), d, J=11.5, 8.5Hz,  $\text{C}_5^{\text{H}}-\text{H}_\text{A}$ ), 3.37 (1H, AB<sub>Q</sub> (B part), d, J=11.5, 6.5Hz,  $\text{C}_5-\text{H}_\text{B}$ ), 4.60 (1H, dd, J=8.5, 6.5Hz,  $\text{C}_4-\text{H}$ ), 6.28 (1H, s,  $\text{C}_2-\text{H}$ ), 6.45-8.07 (4H, m, arom. H), 9.77 (1H, s,  $-\text{COOH}$ ). TLC: Rf value<sup>\*3</sup> 0.52.

\*1 The numbers represent the positions on thiazolidine or

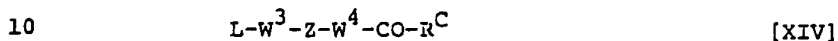


by the same method as (ii) above to yield a compound of the formula [I];

- 5 (vi) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII]

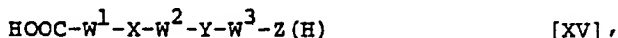


and then with a compound of the formula [XIV]



by the same method as (ii) above to yield a compound of the formula [I], or

- 15 (vii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XV]



and then with a compound of the formula [XVI]



by the same method as (ii) above to yield a compound of the formula [I];

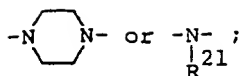
furthermore converting  $R^B$ ,  $R^C$ , X, Y and Z to other functional groups by the general methods, if desired, to obtain a desired compound of the formula [I].

25

17. A composition comprising a compound of the formula [I]

- 1 (4R)-3-(6-carboxyhexanoyl)-2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(7-carboxyheptanoyl)-2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid
- 5 (4R)-3-(13-carboxytridecanoyl)-2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(7-carboxyheptanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-[3-(2-carboxyethylthio)propanoyl]-2-(5-nitrophenyl)-4-thiazolidinecarboxylic acid
- 10 (4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(6-carboxyhexanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- 15 (4R)-3-(9-carboxynonanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(11-carboxyundecanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-[4-(3-carboxypropyloxy)butanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- 20 (4R)-3-[3-(2-carboxyethylsulfonyl)propanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(9-carboxynonanoyl)-2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid
- 25 (4R)-3-(11-carboxyundecanoyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(13-carboxytridecanoyl)-2-(2-acetoxyphenyl)-4-

1



l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, ..., R<sup>20</sup> and R<sup>21</sup> each is R<sup>d</sup>;

5

R<sup>a</sup> is selected from the group consisting of

- (i) hydrogen, lower alkyl and lower alkenyl, and
- (ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkyl-amino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl, sulfamoyl, lower alkylamino-sulfonyl and lower alkylsulfinyl;

10

R<sup>b</sup> is selected from the group consisting of

- (a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
- (ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and
- (iii) carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl and heteroaryloxy-carbonyl;

15

20

- (b)(i) phenyl and naphthyl, and

- (ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,

25

1 was added dropwise under ice-cooling. After the  
2 addition, the reaction mixture was stirred for 1 hour at  
3 the same temperature and for additional 1 hour at room  
4 temperature. The solution was acidified with dilute  
5 hydrochloric acid, extracted with ethyl acetate. The

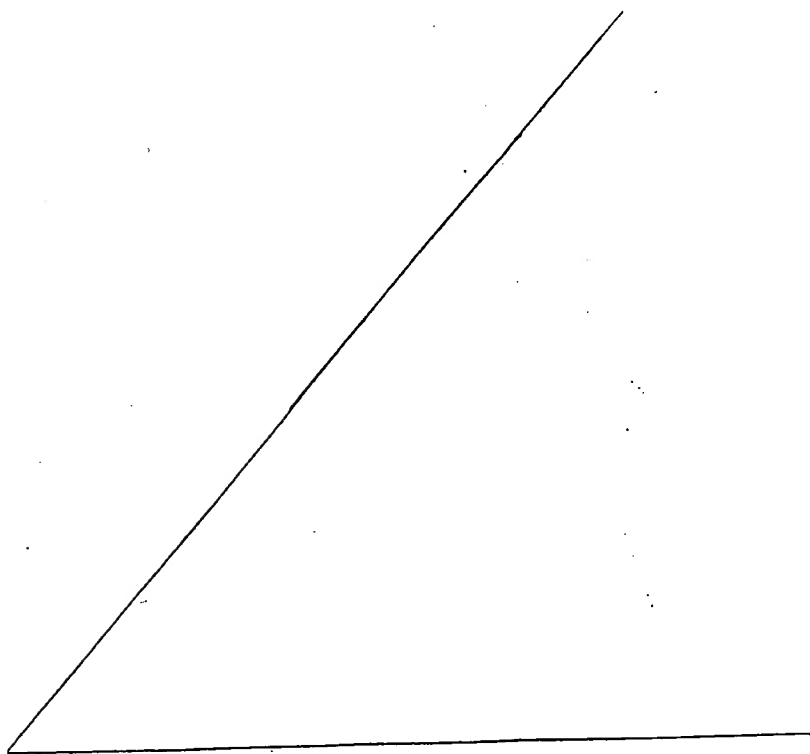
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- 1 (a)(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylamino-sulfonyl, lower alkylthio and lower alkylsulfinyl;
- 5 (b)(i) phenyl and naphthyl, and  
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;
- 10 (c)(i) furyl, thienyl and pyridyl, and  
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl; sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;
- 15 or. salts thereof in an amount sufficient to prevent or relieve diabetes mellitus associated complications consisting of cataracts, neuropathy, nephropathy and retinopathy, and pharmaceutically acceptable excipient(s).
- 20

25 18. A composition comprising a compound of the formula [I]

1 filtered to give the precipitates. The precipitates were  
 dissolved in hot water (100ml), and acidified with  
 concentrated hydrochloric acid. The separated crystals  
 were collected by filtration to give 3.5g (59%) of the  
 5 titled compound: mp 105-112°C;  $[\alpha]_D^{25} +115.0^\circ$  (c=1.0,  
 methanol). IR (nujol,  $\text{cm}^{-1}$ ): 2270 (CN), 1735 (COOH),  
 1640 (CON), 1616 (aromatic), 1195, 790 (aromatic). NMR  
 (DMSO- $d_6$ )  $\delta$ : 0.69-1.66 (6H, m,  $-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$ ),  
 1.70-2.50 (4H, m,  $-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$ ), 2.85-3.66 (4H, m,  
 10  $\text{C}_5\text{-H}$ ), 4.69 (1H, dd,  $J=8.2, 6.0\text{Hz}$ ,  $\text{C}_4\text{-H}$ ), 5.13 (1H, m,  
 $\text{C}_4\text{-H}$ ), 6.16 (1H, s,  $\text{C}_2\text{-H}$ ), 6.43 (1H, s,  $\text{C}_2\text{-H}$ ), 7.3-8.3<sup>\*</sup>  
 (8H, m, arom. H). TLC: Rf value<sup>\*</sup> 0.33.

\* Silica gel, ethyl acetate-chloroform-acetic acid  
 15 (10:5:3).

The compounds shown in Table II were prepared by the  
 same procedure as described above.

The following compounds are also prepared by the same  
 20 procedure as EXAMPLE 2 or 3.

(4R,4'R)-3,3'-(propanedioyl)bis(4-thiazolidinecarboxylic  
 acid)

(4R,4'R)-3,3'-(butanedioyl)bis(2-phenyl)-4-thiazolidine-  
 carboxylic acid)

25 (4R,4'R)-3,3'-(3,3'-sulfinyldipropanoyl)bis[2-(2-hydroxy-  
 phenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(2-hydroxy-  
 phenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedithio)diacetyl]bis[2-(2-hydroxy-

1  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$  and  $R^{26}$  each is  $R^d$ ;

$R^a$  is selected from the group consisting of

- (i) hydrogen, lower alkyl and lower alkenyl, and  
(ii) lower alkyl and lower alkenyl substituted by at least  
5 one substituent selected from the group consisting of lower  
alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower  
alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkyl-  
amino, dialkylamino, acylamino, mercapto, acylmercapto,  
lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-  
carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-  
sulfonyl and lower alkylsulfinyl;

10

$R^b$  is selected from the group consisting of

- (a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and  
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl  
substituted by at least one substituent selected from the  
group consisting of lower alkyl, lower alkenyl, halogeno-  
lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,  
15 acyloxy, halogen, nitro, cyano, amino, lower alkylamino,  
dialkylamino, acylamino, mercapto, acylmercapto, lower  
alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-  
carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-  
sulfonyl and lower alkylsulfinyl, and  
(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,  
aryloxycarbonyl and heteroaryloxycarbonyl;

20

(b) (i) phenyl and naphthyl, and

- (ii) phenyl and naphthyl substituted by at least one  
substituent selected from the group consisting of lower  
alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower  
alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy,  
halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,  
25 acylamino, mercapto, acylmercapto, lower alkylthio, carboxy,  
lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl,  
sulfamoyl, lower alkylsulfonyl and lower alkylsulfinyl;

- 1 (4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-acetoxyphenyl)-  
4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(heptanedioyl)bis[2-(2-furyl)-4-thiazolidine-  
carboxylic acid]
- 5 (4R,4'R)-3,3'-(octanedioyl)bis[2-(2-thienyl)-4-thiazolidine-  
carboxylic acid]  
(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-pyridyl)-4-thiazolidine-  
carboxylic acid]  
(4R,4'R)-3,3'-(decanedioyl)bis[2-(1-naphtyl)-4-thiazolidine-  
10 carboxylic acid]  
(4R,4'R)-3,3'-(hexanedioyl)bis[2-(2-hydroxy-5-sulfamoyl-  
phenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(octanedioyl)bis[2-(3-difluoromethoxyphenyl)-  
4-thiazolidinecarboxylic acid]
- 15 (4R,4'R)-3,3'-(nonanedioyl)bis[2-(4-carboxyphenyl)-4-  
thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(decanedioyl)bis[2-(3-methylsulfinyl-  
phenyl)-4-thiazolidinecarboxylic acid]

20

## EXAMPLE 4

(4R,4'R)-3,3'-(Heptanedioyl)bis[2-(3-nitrophenyl)-4-  
thiazolidinecarboxylic acid] (compound 35)

To a stirred solution of (4R)-2-(3-nitrophenyl)-  
25 4-thiazolidinecarboxylic acid (5.1g) in 11M  
sodium carbonate (40ml), heptanedioyl dichloride (2.1g)  
was added dropwise under ice-cooling. The

- 1 one substituent selected from the group consisting of lower  
alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl,  
heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino,  
guanidino, mercapto, acylamino, acylmercapto, lower alkoxy-  
carbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower  
5 alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;  
(b) (i) phenyl and naphthyl, and  
(ii) phenyl and naphthyl substituted by at least one  
substituent selected from the group consisting of lower  
alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy,  
carboxy, amino, halogen, nitro, cyano, acylamino, mercapto,  
acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy,  
10 lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl,  
lower alkylaminosulfonyl and lower alkylsulfinyl;  
(c) (i) furyl, thienyl and pyridyl, and  
(ii) furyl, thienyl and pyridyl substituted by at least  
one substituent selected from the group consisting of  
lower alkyl, lower alkoxy, lower alkanoyl, acyloxy,  
15 hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino,  
mercapto, acylmercapto, halogeno-lower alkyl, halogeno-  
lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl,  
sulfo, sulfamoyl, lower alkylaminosulfonyl and lower  
alkylsulfinyl;  
20 or salts thereof in an amount sufficient to reduce blood  
pressure and pharmaceutically acceptable excipient(s).  
19. A compound according to claim 1 to 16 for use in a  
method for therapy or prophylaxis.  
20. Use of a compound according to claim 1 to 16 in a  
process for producing pharmaceutical compositions.

25

- 1 (OH), 1720 (COOH), 1618 (CON), 1602 (aromatic), 1245, 1173, 940, 763. NMR (DMSO- $d_6$ ,  $\delta$ ): 2.0-2.7 (4H, m,  $-\text{CH}_2\text{CH}_2-$ ), 3.03 (1H, AB<sub>q</sub> (A part), d, J=11.0, 10.0Hz, C<sub>5</sub>-H<sub>A</sub>), 3.36 (1H, AB<sub>q</sub> (B part), d, J=11.0, 7.0Hz, C<sub>5</sub>-H<sub>B</sub>), 4.61 and 5.07 (1H, 5 dd, J=10.0, 7.0Hz and m, C<sub>4</sub>-H), 6.36 (1H, s, C<sub>2</sub>-H), 6.5-8.0 (4H, arom. H). TLC: Rf value\* 0.35.

\* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

- 10 The compounds shown in Table I and III were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 5.

(4R)-3-(4-carboxy-4-oxobutanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

- 15 (4R)-3-(6-carboxy-3,5-dioxohexanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[4-carboxy-3-(methoxyimino)butanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

20 EXAMPLE 6

(4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 4)

- To a stirred solution of (4R)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (11.3g) in 1M sodium carbonate (80mL), dl-3-methoxycarbonyl-2-methylpropanoyl chloride (3.2g) was added dropwise under ice-cooling.
- 25

- 1 (ethyl acetate);  $[\alpha]_D^{25} +174.1^\circ$  ( $c=1.0$ , methanol). IR (nujol,  $\text{cm}^{-1}$ ): 3330 (OH), 1730 and 1710 (COOH), 1629 (CON), 1280, 1234, 856, 771.

5 The compounds shown in Table I and II were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 6 and 7.

- (4R)-3-[4-(carboxymethyl)benzoyl]-2-(2-hydroxyphenyl)-  
10 4-thiazolidinecarboxylic acid  
(4R)-3-[(4-carboxyphenyl)acetyl]-2-phenyl-4-thiazolidinecarboxylic acid  
(4R)-3-(4-carboxy-3-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid  
15 (4R)-3-(4-carboxy-2-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid  
(4R)-3-(4-carboxy-3-butynoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

20

## EXAMPLE 8

(4R)-3-[3-(N-Hydroxycarbamoyl)propanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid ethyl ester  
(compound 10a)

25

To a stirred solution of (4R)-3-(3-carboxypropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid ethyl ester (compound 9a) (1.06g) and N-methylmorpholine (0.33ml)

1 in 20ml of anhydrous tetrahydrofuran, isobutyl chloro-  
 formate (0.39ml) was added dropwise at  $-15^{\circ}\text{C}$ , and stirred  
 for additional 2 hours at this temperature. To this  
 solution, the methanol solution of hydroxylamine (0.3g)  
 5 was added dropwise at  $-50^{\circ}\text{C}$ . The reaction mixture was  
 stirred for 1 hour at room temperature, acidified with  
 N hydrochloric acid, and extracted  
 with ethyl acetate. The organic layer was washed with  
 saturated sodium chloride solution, dried over anhydrous  
 10 magnesium sulfate, and concentrated in vacuo. The  
 residual oil was purified by silica gel column chromatog-  
 raphy to give 0.7g (63%) of the titled compound. IR  
 (KBr,  $\text{cm}^{-1}$ ) 3220, 1727, 1625, 1595, 1200, 1092, 753.  
 NMR (acetone- $d_6$ ,  $\delta$ ): 1.24 (3H, t,  $J=7.5\text{Hz}$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ),  
 15 2.17-3.07 (4H, m,  $\text{CO}-(\text{CH}_2)_2\text{CO}$ ), 3.30 (1H,  $\text{AB}_q$  (A part), d,  
 $J=10.0$ , 2.0Hz,  $\text{C}_5\text{-H}_A$ ), 3.47 (1H,  $\text{AB}_q$  (B part), d,  $J=10.0$ ,  
 7.0Hz,  $\text{C}_5\text{-H}_B$ ), 4.14 (2H, q,  $J=7.5\text{Hz}$ ,  $\text{CO}_2\text{CH}_2$ ), 5.18 (1H,  
 dd,  $J=2.0$ , 7.0Hz,  $\text{C}_4\text{-H}$ ), 6.40 (1H, s,  $\text{C}_2\text{-H}$ ), 6.88-7.27  
 (4H, m, arom. H), 8.60 (2H, br. s,  $\text{NHOH}$ ), 9.77 (1H, br. s,  
 20  $\text{OH}$ )

The compounds shown in Table I were prepared by the same  
 procedure as described above.

25

## EXAMPLE 9

(4R,4'R)-3,3'-(Nonanedioyl)bis[2-(3-nitrophenyl)-4-  
 thiazolidinecarboxylic acid methyl ester] (compound 46)

1           To a stirred solution of (4R,4'R)-3,3'-(nonanedioyl)bis-  
[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]  
(compound 47) (3.3g) in ethyl acetate (50ml), 2% ether  
solution of diazomethane was added dropwise until the  
5           yellow color of diazomethane was not disappeared, and  
stirred continuously for 30 minutes. The reaction mixture  
was concentrated in vacuo to give 3.3g (96%) of the titled  
compound: mp 61-63°C (benzene);  $[\alpha]_D^{23} +79.4^\circ$  (c=1.0,  
methanol). IR (KBr,  $\text{cm}^{-1}$ ): 1740, 1660, 1530, 1350,  
10           1198, 725.

## EXAMPLE 10

(4R)-3-[(2-Carboxymethylthio-3-phenyl)propanoyl]-4-  
thiazolidinecarboxylic acid (compound 75a and 75b)

15           (4R)-3-[(2-Mercapto-3-phenyl)propanoyl]-4-thiazolidine-  
carboxylic acid (1.0g), potassium carbonate (0.7g),  
chloroacetic acid (0.2g) and potassium iodide (0.05g)  
were dissolved in water (5ml), and stirred for 6 hours  
20           at room temperature. The reaction mixture was acidified  
with 5N hydrochloric acid and extracted with ethyl acetate.  
The organic layer was washed with saturated sodium chloride  
solution, dried over anhydrous magnesium sulfate and  
concentrated in vacuo. The titled compounds (75a and 75b)  
25           were separated from the oily residue by silica gel  
column chromatography.

	75a	75b
1		
1	yield 0.4g (37%)	0.5g (47%)
	$[\alpha]_D^{25}$ -52.2° (c=1.2, MeOH)	-60.4° (c=1.0, MeOH)
5	IR (neat, cm <sup>-1</sup> ) 1720, 1620, 1422, 1217, 756	1722, 1620, 1420, 1215, 755
10	NMR (CDCl <sub>3</sub> , δ) 2.67-3.63 (6H, m, -S-CH <sub>2</sub> -CO <sub>2</sub> H, C <sub>5</sub> -H, -CH <sub>2</sub> -Ph), 3.83-4.83 (3H, m, -CO-CH <sub>2</sub> -S-, C <sub>2</sub> -H), 4.98 (1H, dd, J=4.5, 6.5Hz, C <sub>4</sub> -H), 7.22 (5H, s, -C <sub>6</sub> H <sub>5</sub> ) 9.55 (-CO <sub>2</sub> H)	2.70-3.50 (6H, m, -S-CH <sub>2</sub> -CO <sub>2</sub> H, C <sub>5</sub> -H, -CH <sub>2</sub> -Ph), 4.00-4.57 (3H, m, -CO-CH <sub>2</sub> -S-, C <sub>2</sub> -H) 5.02 (1H, dd, J=4.5, 9.5Hz, C <sub>4</sub> -H), 7.23 (5H, s, -C <sub>6</sub> H <sub>5</sub> ) 10.00 (-CO <sub>2</sub> H)

15

The compounds shown in Table IV were prepared by the same procedure as described above.

## EXAMPLE 11

20 (4R)-3-[(Carboxymethylamino)acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 81)

(4R)-3-Chloroacetyl-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (6g) was added to a stirred solution of glycine (1.5g) in N sodium hydroxide (80ml), and stirred  
25 overnight at room temperature. The solution was adjusted to pH 1.5 by 20% hydrochloric acid and washed with ethyl acetate. The aqueous layer was adjusted to pH 3.2, and

1 the separated crystals were collected by filtration to  
 3.28g (48.2%) of the titled compound: mp 181-182°C (dec.)  
 (water);  $[\alpha]_D^{24} +271.2^\circ$  (c=0.5, MeOH). IR (KBr,  $\text{cm}^{-1}$ ):  
 3400, 3200, 1740, 1672, 1560, 1440, 1380, 1335, 1212,  
 5 752, 648, NMR ( $\text{K}_2\text{CO}_3$  in  $\text{D}_2\text{O}$ ,  $\delta$ ): 3.0-4.3 (6H, m,  $\text{C}_5\text{-H}$ ,  
 $\text{COCH}_2\text{NHCH}_2\text{CO}_2\text{H}$ ), 6.33 and 6.43 (1H, each s,  $\text{C}_2\text{-H}$ ), 6.6-  
 7.3 (3H, m, arom. H), 7.82 (1H, br. d,  $J=8\text{Hz}$ , arom. H),  
 9.0-10.3 (2H, br. s,  $-\text{OH}$ ,  $-\text{CO}_2\text{H}$ ).

10 The compounds shown in Table V were prepared by the  
 same procedure as described above.

#### EXAMPLE 12

(2S)-1-[[[(2S)-2-Bis(ethoxycarbonylmethyl)amino]propanoyl]-  
 15 2-pyrrolidinecarboxylic acid benzyl ester (compound 88)

Ethyl bromoacetate (0.92g) was added dropwise under  
 ice-cooling to a stirred solution of L-alanyl-L-proline  
 benzyl ester p-toluenesulfonate (2.24g) and triethylamine  
 20 (1.53ml) in dry methylenechloride. After the addition,  
 the reaction mixture was stirred for 2 hours at room  
 temperature, refluxed for another 5 hours, and washed with  
 water and saturated sodium chloride solution. The organic  
 layer was dried over anhydrous magnesium sulfate and concentrated  
 25 in vacuo. The residual oil was purified by silica gel column  
 chromatography to give 1.02g (44.8%) of the titled

- 1 compound:  $[\alpha]_D^{24} -67.9^\circ$  ( $c=1.2$ , MeOH). IR (neat,  $\text{cm}^{-1}$ ):  
 3460, 1742, 1642, 1428, 1180. NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.23 (6H, t,  
 J=7Hz,  $-\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.25 (3H, d, J=7.2Hz,  $\text{CO}-\text{CH}-\text{N}$  ), 1.67-  
 5 2.40 (4H, m,  $\text{C}_3\text{-H}$  and  $\text{C}_4\text{-H}$ ), 3.57 (4H, s,  $-\text{N}-\text{CH}_2\text{CO}_2\text{Et}$ ),  
 3.50-4.00 (2H, m,  $\text{C}_5\text{-H}$ ), 4.13 (4H, q, J=7Hz,  $-\text{COCH}_2\text{CH}_3$ ),  
 4.10-4.67 (2H, m,  $\text{C}_2\text{-H}$  and  $-\text{CO}-\text{CH}-\text{N}$ ), 5.03, 5.20 (2H, AB<sub>q</sub>,  
 10 J=12Hz,  $-\text{CH}_2\text{-Ph}$ ), 7.30 (5H, s,  $-\text{C}_6\text{H}_5$ ).

The compounds shown in Table V were prepared by the same procedure as described above.

15

## EXAMPLE 13

(2S)-1-[[[(2S)-Bis(ethoxycarbonylmethyl)amino]propanoyl]-  
 2-pyrrolidinecarboxylic acid (compound 86)

- (2S)-1-[[[(2S)-2-bis(ethoxycarbonylmethyl)amino]propanoyl]-  
 20 2-pyrrolidinecarboxylic acid benzyl ester (compound 88)  
 (0.50g) was dissolved in ethanol (10ml), and hydrogenated  
 with 10% palladium on charcoal catalyst (50mg). The  
 titled compound was obtained as a colorless oil. Yield  
 0.40g (quant. yild);  $[\alpha]_D^{24} -52.2^\circ$  ( $c=1.1$ , MeOH). IR  
 25 (neat,  $\text{cm}^{-1}$ ): 1742, 1640, 1442, 1190, 1130, 752. NMR  
 ( $\text{CDCl}_3$ ,  $\delta$ ): 1.23 (6H, t, J=7Hz,  $-\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.25 (3H, d,  
 J=7.2Hz,  $\text{COCH}-\text{N}$  ), 1.67-2.50 (4H, m,  $\text{C}_3\text{-H}$  and  $\text{C}_4\text{-H}$ ),  
 5.03, 5.20 (2H, AB<sub>q</sub>,  $-\text{CH}_2\text{-Ph}$ ), 7.30 (5H, s,  $-\text{C}_6\text{H}_5$ ).

- 1 3,53 (4H, s,  $\text{N-CH}_2\text{-CO}_2\text{Et}$ ), 3.50-4.00 (2H, m,  $\text{C}_5\text{-H}$ ), 4.10  
 (4H, q,  $\text{J}=7\text{Hz}$ ,  $\text{-CO}_2\text{CH}_2\text{CH}_3$ ), 4.10-4.33 (1H, m,  $\text{-COCH(N)-}$ ,  
 $\text{CH}_3$ )  
 4.47 (1H, dd,  $\text{J}=6.5$ ,  $5.0\text{Hz}$ ,  $\text{C}_2\text{-H}$ ), 9.20 (1H, br. s,  $\text{-CO}_2\text{H}$ ).

5

The compounds shown in Table V were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 12 and 13.

- (2S)-1-[[4-(1-carboxy-3-phenylpropyl)amino]benzoyl]-2-pyrrolidinecarboxylic acid.  
 10 (4R)-3-[[4-(1-carboxy-3-phenylpropyl)amino]benzoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

## EXAMPLE 14

- 15 (2S)-1-[[[(2S)-2-(N-Ethoxycarbonylmethyl-N-phenylacetyl)-amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (compound 90)

- Phenylacetyl chloride (0.44ml) was added dropwise at  
 20 room temperature to a stirred solution of (2S)-1-[[[(2S)-2-(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (1.1g) and triethylamine (0.47ml) in dry acetone (15ml). After the addition, the reaction mixture was stirred for 1 hour at the same temperature,  
 25 and the precipitate was removed by filtration. The filtrate was evaporated in vacuo, and the residual oil was dissolved in ethyl acetate, and washed with water and

1 saturated sodium chloride solution. The organic layer  
was dried over anhydrous magnesium sulfate, and evaporated  
in vacuo. The residual oil was purified by silica gel  
column chromatography to give 1.3g (89%) of the titled  
5 compound: mp 110-110.5°C (benzene-hexane);  $[\alpha]_D^{24}$  -114.0°  
(c=1.0, MeOH). IR (KBr,  $\text{cm}^{-1}$ ): 3460, 1739, 1635, 1436,  
1200, 1166. NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.23 (3H, d,  $J=7\text{Hz}$ ,  $-\text{CO}-\text{CH}-\text{N}$   
 $\text{CH}_3$ )  
1.28 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.67-2.50 (4H, m,  $\text{C}_3-\text{H}$  and  
10  $\text{C}_4-\text{H}$ ), 3.60 (2H, s,  $-\text{COCH}_2\text{Ph}$ ), 3.33-3.90 (2H, m,  $\text{C}_5-\text{H}$ ),  
4.16 (2H, q,  $J=7\text{Hz}$ ,  $-\text{COCH}_2\text{CH}_3$ ), 4.23 (2H, s,  $-\text{N}-\text{CH}_2\text{CO}_2\text{Et}$ ),  
4.30-4.60 (1H, m,  $\text{C}_2-\text{H}$ ), 5.03, 5.23 (2H, ABq,  $J=12.5\text{Hz}$ ,  
 $-\text{CO}_2\text{CH}_2\text{Ph}$ ), 5.58 (1H, q,  $J=7\text{Hz}$ ,  $-\text{COCH}-\text{N}$   
 $\text{CH}_3$ )  
15  $-\text{COCH}_2\text{C}_6\text{H}_5$ ), 7.30 (5H, s,  $-\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$ ).

The compounds shown in Table V were prepared by the same procedure as described above.

## 20

EXAMPLE 15

(2S)-1-[(2S)-2-[(1-Carboxy-3-phenylpropyl)thio]propanoyl]-2-pyrrolidinecarboxylic acid (compound 79)

(2S)-1-[(2S)-2-Mercaptopropanoyl]-2-pyrrolidine-  
25 carboxylic acid (2.0g), potassium carbonate (2.3g) and 2-  
bromo-4-phenylbutanoic acid (2.9g) were dissolved in water  
(40ml), and stirred overnight at room temperature. The

- 1 reaction mixture was acidified with 6N hydrochloric acid,  
and extracted with ethyl acetate. The organic layer was  
washed with saturated sodium chloride solution, dried  
over anhydrous magnesium sulfate, and concentrated in vacuo.  
5 The residual oil was purified by silica gel column chromatography to give 2.3g (62%) of the titled compound:  $[\alpha]_D^{23}$   
-82.2° (c=1.2, MeOH). IR (KBr,  $\text{cm}^{-1}$ ): 1740, 1720, 1610, 1455,  
1438, 1185, 748, 700.
- 10 The compounds shown in Table IV were prepared by the  
same procedure as described above.

## EXAMPLE 16

- 15 1-[[[(1-Carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxy-  
phenyl)-5-pyrrolidinecarboxylic acid (compound 99)

- 1-(Chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidine-  
carboxylic acid [mp 204-206°C(dec.),  $[\alpha]_D^{24}$  +24.5° (c=1.2,  
MeOH)] (2.8g) was added to a stirred solution of 2-amino-  
20 4-phenylbutanoic acid (1.8g) in N sodium hydroxide (40ml).  
The reaction mixture was stirred overnight at room  
temperature. The solution was adjusted to pH 1.5 by 20%  
hydrochloric acid, and washed with ethyl acetate. The  
aqueous layer was adjusted to pH 3.0, and the separated  
25 solid was collected by filtration to give 1.0g (24%) of  
the titled compound. IR (nujol,  $\text{cm}^{-1}$ ): 3425, 1735, 1625,  
1588.

1 The compounds shown in Table V were prepared by the same  
procedure as described above.

5 In EXAMPLES and TABLES I, II, III, IV and V, "a" and "b"  
of compound No. represent diastereoisomers each other.  
TABLES I, II, III, IV and V show various compounds and  
their physical constants including the compounds specified  
in EXAMPLES.

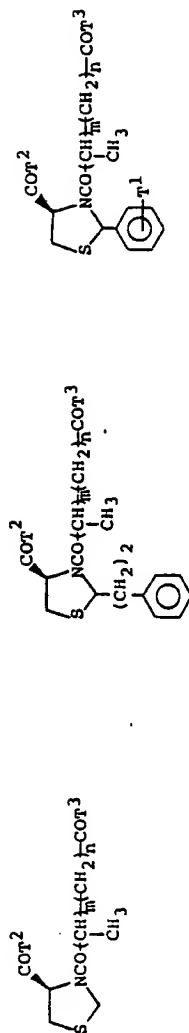
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Table I



Compound No. 1

Compound No. 2a and 2b

Compound 3-32

Compd. No.	T <sup>1</sup>	T <sup>2</sup>	T <sup>3</sup>	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf *2 value (SiO <sub>2</sub> )
										Sampling <sup>1</sup> method	-1 cm	
1		OH	OH	0	6	1	55	oil	-84.3 (0.8, MeOH, 26)	C	1720, 1605, 1420, 1190, 1015, 880	0.39
2a		OH	OH	0	3	5	26	oil	-19.8 (1.1, MeOH, 24)	C	1733, 1710, 1650, 1600, 1410, 1240, 1040	0.60 <sup>3</sup>
2b		OH	OH	0	3	5	51	oil	-113.8 (1.1, MeOH, 24)	C	1730, 1650, 1610, 1410, 1240, 1042	0.55 <sup>3</sup>
3	2-OH	OH	OH	0	1	1	65	154.0-154.5 (dec.) (H <sub>2</sub> O)	+201.4 (0.7, MeOH, 25)	B	3340, 1725, 1625, 1600, 1460, 1430, 1235, 1100, 915, 770	0.25
4	2-OH	OH	OMe	1	1	6	44	oil	+161.6 (1.0, MeOH, 25)	A <sup>1</sup>	3380, 1723, 1624, 1235, 1200, 1174, 764	0.51
5	2-OH	OH	OH	1	1	7	75	163-164 (dec.) (EtOAc)	+174.1 (1.0, MeOH, 25)	B	3330, 1730, 1710, 1629, 1280, 1234, 856, 771	0.41

Table-continued

Compd. <sup>†</sup> No.	T <sup>1</sup>	T <sup>2</sup>	T <sup>3</sup>	m	n	Method of prep. (Examp. No.)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	Sampling <sup>1</sup> method	IR spectrum		Rf <sup>2</sup> value (SiO <sub>2</sub> )
										cm <sup>-1</sup>	cm <sup>-1</sup>	
6	2-OH	OH	OH	0	2	1	190-191 (dec.) (EtOAc-MeOH)	+181.6 (1.0, MeOH, 27)	B	3210, 1720, 1618, 1602, 1245, 1173, 940, 763		0.35
7	2-OH	OH	OH	0	2	6	165-166 (dec.) (EtOAc)	+164.5 (1.0, MeOH, 25)	A	3370, 1750, 1693, 1635, 1215, 1165, 755		0.47
8a	2-OH	OEt	OH	0	2	5	181-182 (EtOAc)	-2.8 (0.5, MeOH, 21)	A	3310, 1727, 1703, 1637, 1595, 1235, 1190, 745		0.55
8b	2-OH	OEt	OH	0	2	5	116-118 (EtOAc)	-311.6 (0.5, MeOH, 21)	A	3370, 1735, 1708, 1635, 1597, 1220, 1180, 760		0.55
9a	2-OH	OH	NIHOH	0	2	7	172-173 (dec.) (EtOH-H <sub>2</sub> O)		A	3375, 3290, 1720, 1657, 1625, 1590, 1240, 1088, 748		0.22
9b	2-OH	OH	NIHOH	0	2	7	amorph.		A	3220, 1717, 1655, 1625, 1595, 1225, 1092, 752		0.33
10a	2-OH	OEt	NIHOH	0	2	8	amorph.		A	3220, 1727, 1625, 1595, 1200, 1092, 753		0.25 <sup>4</sup>
10b	2-OH	OEt	NIHOH	0	2	8	amorph.					0.32 <sup>4</sup>
11 <sup>5</sup>	2-OH	OH	OH	1	2	6	amorph.	+55.5 (0.8, MeOH, 24)	B	1738, 1630, 1585, 1310, 1258, 750		
11a <sup>5</sup>	2-OH	OH	OH	1	2	6	205-207 (dec.) (benzene)	+94.6 (0.5, MeOH, 23)	B	3110, 1730, 1625, 1610, 1192, 1121, 758		
12a	2-OH	OH	OH	1	2	7	168-170 (dec.) (acetone- cyclohexane)	+168.0 (0.4, MeOH, 23)	A	3370, 1718, 1625, 1598, 758		0.25 <sup>4</sup>
12b	2-OH	OH	OH	1	2	7	163-164 (dec.) (acetone- cyclohexane)	+149.2 (0.4, MeOH, 23)	A	3300, 1720, 1708, 1615, 1598, 1242, 753		0.25 <sup>4</sup>
13	2-OH	OH	OH	0	3	5	161-162 (dec.) (H <sub>2</sub> O)	+153.8 (0.5, MeOH, 24)	B	3190, 1713, 1632, 1598, 1253, 1098, 943, 760		0.38
14	2-OH	OH	OEt	0	3	6	157-158 (dec.) (EtOAc-benzene)	+145.6 (1.0, MeOH, 25)	A	3340, 1725, 1638, 1597, 1218, 1120, 768 <sup>4</sup>		0.48
15	H	OH	OH	0	3	5	139-140 (EtOAc-MeOH)	+106.3 (1.0, MeOH, 24)	B	3170, 1753, 1709, 1631, 1423, 1177, 729		0.39

Table-continued

Compd. No.	T <sup>1</sup>	T <sup>2</sup>	T <sup>3</sup>	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		R <sub>f</sub> #2 value (SiO <sub>2</sub> )
										Sampling <sup>1</sup> method	cm <sup>-1</sup>	
16	4-CN	OH	OH	0	3	5	59	190-191 (EtOAc-MeOH)	+137.7 (1.0, MeOH, 24)	B	2225, 1710, 1665, 1412, 1258	0.31
17	2-OH	OH	OH	0	4	1	62	amorph.	+115.6 (1.0, MeOH, 24)	B	3300, 1700, 1622, 1595, 760, 723	0.43
18	2-OH	OH	OH	0	5	1	60	158-159 (dec.) (EtOAc)	+128.6 (0.5, MeOH, 25)	B	3300, 1710, 1620, 1595, 1280, 1095, 895, 850, 760	0.47
19	H	OH	OH	0	6	1	33	oil	+80.5 (1.0, MeOH, 24)			0.50
20	2-OH	OH	OH	0	6	1	61	155-157 (dec.) (EtOAc)	+134.1 (0.5, MeOH, 27)	B	3220, 1710, 1620, 1600, 1415, 1235, 1172, 950, 760	0.52
21	2-OH	OH	OH	0	7	1	63	153-154 (dec.) (EtOAc)	+70.9 (0.5, MeOH, 26)	B	3220, 1705, 1620, 1600, 1415, 1235, 1173, 1090, 830, 760	0.55
22	3-NO <sub>2</sub>	OH	OH	0	7	1	45	oil	+72.1 (0.4, MeOH, 27)	C	1710, 1615, 1525, 1405, 1350, 1095, 735	0.56
23	3-NO <sub>2</sub>	OH	OH	0	7	6	79	oil	+71.8 (1.0, MeOH, 23)	C	1735, 1663, 1620, 1513, 1352, 1240, 1190, 728	0.57
24	2-F	OH	OH	0	7	1	53	oil	+69.9 (0.5, MeOH, 23)	C	1730, 1660, 1625, 1587, 1228, 1043, 756	0.57
25	3-F	OH	OH	0	7	1	50	oil	+63.4 (0.5, MeOH, 23)	C	1730, 1655, 1610, 1590, 1243, 1042, 775	0.57
26	4-F	OH	OH	0	7	1		oil	+57.9 (0.8, MeOH, 23)			0.51 <sup>4</sup>
27	2-Cl 5-NO <sub>2</sub>	OH	OH	0	7	1	45	amorph.	+108.3 (0.5, MeOH, 23)	A	1720, 1660, 1580, 1526, 1240, 1050, 745	0.57

Table-continued

Compd. <sup>†</sup> No.	T <sup>1</sup>	T <sup>2</sup>	T <sup>3</sup>	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf <sup>*2</sup> value (SiO <sub>2</sub> )
										Sampling <sup>*1</sup> method	cm <sup>-1</sup>	
28	2-OH	OH	OH	0	8	1	58	oil	+100.3 (1.0, MeOH, 24)	C	1710, 1620, 1600, 1410, 1230, 1090, 850, 760	0.58
29	2-OH	OH	OH	0	10	1	55	123-124 (EtOAc-cyclo- hexane)	+120.4 (0.5, MeOH, 25)	B	3320, 1705, 1620, 1595, 1410, 1233, 1090, 943, 850, 760	0.61
30	3-CN	OH	OH	0	10	1	56	oil	+56.4 (0.3, MeOH, 23)			0.56 <sup>*4</sup>
31	2-OH	OH	OH	0	12	1	59	amorph.	+101.4 (1.0, MeOH, 24)	B	3280, 1700, 1620, 1575, 760, 722	0.52
32	3-CN	OH	OH	0	12	1	43	oil	+61.7 (0.6, MeOH, 23)			0.53 <sup>*4</sup>

<sup>†</sup> a and b represent diastereoisomers of the compound.

<sup>\*1</sup> A: KBr disk, B: nujol mull, C: neat.

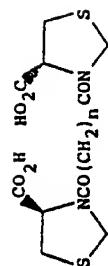
<sup>\*2</sup> EtOAc-CHCl<sub>3</sub>-AcOH (10:5:3).

<sup>\*3</sup> CHCl<sub>3</sub>-EtOH-AcOH (10:2:1).

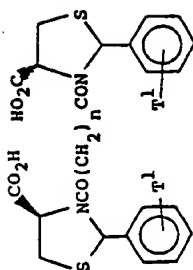
<sup>\*4</sup> EtOAc-CHCl<sub>3</sub>-AcOH (7:5:1).

<sup>\*5</sup> Dicyclohexylamine salt.

Table II



Compound No. 38



Compound No. 33-37, 39-62

Compd. No.	T <sup>1</sup>	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		R <sub>F</sub> +2 value (SiO <sub>2</sub> )
							Sampling*1 method	cm <sup>-1</sup>	
33	2-OH	4	2	73	124-128 (MeOH)	+182.2 (1.0, DMF, 24)	B	3280, 1726, 1620, 1596, 775,	0.23
34	2-OH	5	2	67	oil	+106.1 (0.5, MeOH, 26)	C	1725, 1625, 1600, 1410, 1235, 1095, 1045, 850, 765	0.27
35	3-NO <sub>2</sub> <sup>5</sup>	5	4	69	111-113 (dec.) (H <sub>2</sub> O)	+88.2 (0.5, MeOH, 25)	B	1635, 1585, 1520, 1355 1095, 730	0.28
36	3-CN	5	3	59	105-112 (H <sub>2</sub> O)	+115.0 (1.0, MeOH, 25)	B	2270, 1735, 1640, 1610, 1195, 790	0.33
37	4-CN	5	3	52	amorph.	+148.2 (0.9, MeOH, 25)	B	2255, 1731, 1655, 1620, 785	0.32
38		6	2	77	oil	-124.5 (0.5, MeOH, 26)	C	1720, 1580, 1410, 1180, 1015, 880	0.09
39	H	6	2	79	amorph.	+97.4 (1.0, MeOH, 24)	B	1720, 1625, 1585, 732	0.42

Table-continued

Compd. No.	T <sup>1</sup>	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	Sampling <sup>1</sup> method	IR spectrum		Rf <sup>2</sup> value (SiO <sub>2</sub> )
								cm <sup>-1</sup>		
40	2-OH	6	2	86	amorph.	+123.6 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1230, 1090, 855, 765	0.34	
41	3-NO <sub>2</sub>	6	2	56	amorph.	+97.5 (0.5, MeOH, 21)	B	1730, 1650, 1605, 1520, 1345, 1095, 730	0.34	
42	3-CN	6	2	58	amorph.	+98.3 (0.9, MeOH, 25)	B	2250, 1730, 1640, 1615, 1200, 790	0.38	
43	4-CN	6	2	41	amorph.	+130.2 (0.9, MeOH, 25)	B	2248, 1729, 1650, 1618, 790	0.36	
44	2-OH	7	2	75	amorph.	+142.7 (0.5, MeOH, 26)	B	1720, 1620, 1600, 1410, 1230, 1173, 1090, 855, 763	0.40	
45	2-NO <sub>2</sub>	7	2	47	amorph.	+191.2 (0.6, MeOH, 25)	B	1735, 1655, 1515, 1345, 1190, 730	0.38	
46	3-NO <sub>2</sub>	7	9	96	61-63 (benzene)	+79.4 (1.0, MeOH, 23)	A	1740, 1660, 1530, 1350, 1198, 725	0.57	
47	3-NO <sub>2</sub>	7	2	82	amorph.	+96.2 (0.5, MeOH, 27)	B	1725, 1615, 1520, 1445, 1350, 1095, 730	0.41	
48	4-NO <sub>2</sub>	7	2	53	amorph.	+118.5 (0.5, MeOH, 25)	B	1730, 1650, 1600, 1510, 1345, 1185, 1110, 735	0.48	
49	3-CN	7	3	65	amorph.	+112.1 (1.1, MeOH, 25)	B	2250, 1729, 1640, 1610, 790	0.41	
50	2-F	7	4	85	140-220 (dec.) (H <sub>2</sub> O)	+117.5 (1.0, MeOH, 24)	A	1580, 1225, 1173, 758	0.50	
51	3-F	7	4	88	195-210 (dec.) (H <sub>2</sub> O)	+103.9 (0.5, MeOH, 25)	A	1590, 1238, 1142, 767	0.50	
52	4-F	7	2	76	oil	+75.8 (1.0, MeOH, 23)			0.39 <sup>3</sup>	

Table-continued

Compd. No.	T <sup>1</sup>	Method			mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	Sampling <sup>1</sup> method	IR spectrum cm <sup>-1</sup>	Rf <sup>2</sup> value (SiO <sub>2</sub> )
		n	of prep. (No.)	Yield (%)					
53	2-Cl 5-NO <sub>2</sub>	7	2	79	amorph.	+167.9 (0.5, MeOH, 23)	A	1725, 1640, 1575, 1520, 1342, 1047, 740	0.51
54	2-OH 5-SO <sub>2</sub> NH <sub>2</sub>	7	2	75	amorph.	+140.9 (0.6, MeOH, 23)	B	1725, 1620, 1595, 1310, 1150, 930	0.42 <sup>4</sup>
55	2-OH	8	2	68	amorph.	+122.1 (1.0, MeOH, 24)	B	3300, 1730, 1628, 1575, 767, 725	0.45
56	3-CN	8	2	47	amorph.	+104.6 (1.0, MeOH, 25)	B	2245, 1726, 1630, 1610, 790	0.37
57	3-NO <sub>2</sub>	8	2	84	amorph.	+102.2 (0.5, MeOH, 25)	A	1735, 1620, 1523, 1190, 728	0.47
58 <sup>5</sup>	3-NO <sub>2</sub>	8	4	74	amorph.	+93.9 (0.5, MeOH, 23)	A	1597, 1520, 1269, 1096, 723	
59	2-OH	10	2	61	99-100.5 (dec.) (EtOAc-benzene)	+124.7 (0.5, MeOH, 27)	B	3300, 1740, 1620, 1600, 1565, 1230, 1160, 1090, 895, 770	0.49
60 <sup>5</sup>	3-CN	10	4	63	190-195 (H <sub>2</sub> O)	+109.3 (0.5, H <sub>2</sub> O, 23)	B	3400, 2240, 1640, 1600, 1208, 778, 720	
61	2-OH	12	2	66	amorph.	+69.5 (1.0, MeOH, 24)	B	3300, 1728, 1630, 1590, 762, 725	0.45
62 <sup>5</sup>	3-CN	12	4	52	amorph.	+104.2 (0.5, MeOH, 23)	B	3400, 2225, 1605, 1320, 1207, 775, 720	0.46 <sup>3</sup>

<sup>1</sup> A: KBr disk, B: mull, C: neat.<sup>2</sup> EtOAc-CHCl<sub>3</sub>-AcOH (10:5:1).<sup>3</sup> EtOAc-CHCl<sub>3</sub>-AcOH (7:5:1).<sup>4</sup> CHCl<sub>3</sub>-MeOH-AcOH (3:1:1).<sup>5</sup> Disodium salt.<sup>6</sup> Dimethyl ester.

Table III



Compound No. 63-68

Compound No. 69-71

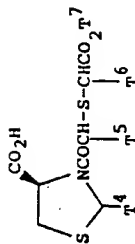
Compd. No.	T <sup>1</sup>	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> , deg. (c, solv., °C)	IR spectrum		Rf. #2 value (SiO <sub>2</sub> )
							Sampling*1 method	cm-1	
63	2-OH	-CH <sub>2</sub> COCH(COCH <sub>3</sub> )-	5	31	amorph.	+149.2 (1.2, MeOH, 25)	B	1743, 1720, 1630, 1600, 1238	0.38 <sup>3</sup>
64	2-OH	-CH <sub>2</sub> -O-CH <sub>2</sub> -	1	35	amorph.	+138.6 (1.1, MeOH, 25)	A	3300, 1726, 1640, 1453, 1234, 1142	0.24 <sup>4</sup>
65	3-NO <sub>2</sub>	{CH <sub>2</sub> } <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	1	36	amorph.	+81.7 (0.9, MeOH, 24)	A	3400, 1702, 1618, 1525, 1400, 1347	0.55 <sup>3</sup>
66	2-OH	{CH <sub>2</sub> } <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -	1	33	136-137 (EtOAc)	+147.6 (0.5, MeOH, 25)	B	3320, 1750, 1710, 1625, 1595, 1235, 1110, 855, 770	0.28
67	2-OH	{CH <sub>2</sub> } <sub>2</sub> -S-(CH <sub>2</sub> ) <sub>2</sub> -	1	40	159-160 (dec.) (EtOAc)	+136.4 (0.5, MeOH, 27)	B	3360, 1710, 1627, 1599, 1435, 1235, 1099, 852, 763	0.42
68	2-OH	{CH <sub>2</sub> } <sub>2</sub> -S-(CH <sub>2</sub> ) <sub>2</sub> -S-(CH <sub>2</sub> ) <sub>2</sub> -	1	35	amorph.	+78.1 (1.0, MeOH, 24)	B	3300, 1715, 1627, 1590, 760	0.31
69	3-NO <sub>2</sub>	{CH <sub>2</sub> } <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -	2	44	amorph.	+106.9 (1.1, MeOH, 24)	A	3425, 1730, 1640, 1525, 1400, 1350	0.38 <sup>3</sup>

Table-continued

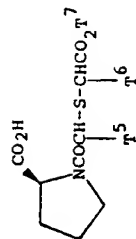
Compd. No.	T <sup>1</sup>	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf value <sup>2</sup> (SiO <sub>2</sub> )
							Sampling <sup>*1</sup> method	cm <sup>-1</sup>	
70	2-OH	$\text{-(CH}_2\text{)}_2\text{-O-(CH}_2\text{)}_2\text{-}$	2	47	amorph.	+83.0 (0.5, MeOH, 26)	B	1720, 1625, 1600, 1230, 1090, 850, 760	0.15
71	2-OH	$\text{-(CH}_2\text{)}_2\text{-S-(CH}_2\text{)}_2\text{-}$	2	53	amorph.	+129.3 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1420, 1230, 1093, 852, 763	0.30

<sup>\*1</sup> A: KBr disk, B: nujol mull.<sup>\*2</sup> EtOAc-CHCl<sub>3</sub>-AcOH (10:5:3).<sup>\*3</sup> EtOAc-EtOH<sup>2</sup>-AcOH (40:1:1).<sup>\*4</sup> CHCl<sub>3</sub>-EtOH-AcOH (10:2:1).

Table IV



Compound No. 72-76



Compound No. 77-80

Compd. No.	T <sup>4</sup>	T <sup>5</sup>	T <sup>6</sup>	T <sup>7</sup>	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf value (SiO <sub>2</sub> )
									Sampling*1 method	cm <sup>-1</sup>	
72a	H	CH <sub>3</sub>	Ph	H	10	30	151-153 (EtOAc)	+8.6 (1.0, MeOH, 23)	A	3030, 1737, 1720, 1615, 1413, 1215, 1150, 717	0.26 <sup>3</sup>
72b	H	CH <sub>3</sub>	Ph	H	10	49	oil	-161.5 (1.0, MeOH, 23)	C	1735, 1623, 1413, 1243, 1170, 1043, 699	0.22 <sup>3</sup>
73		H	CH <sub>2</sub> CH <sub>2</sub> Ph	H	10	81	amorph.	+122.1 (1.2, MeOH, 25)	A	1720-1710, 1625, 1600, 1400, 1235, 752, 698	0.74
74	H	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> Ph	H	10	52	amorph.	-97.9 (1.1, MeOH, 25)	A	1720, 1620, 1415, 750, 700	0.65
75a	H	CH <sub>2</sub> Ph	H	H	10	37	oil	-52.2 (1.2, MeOH, 25)	C	1720, 1620, 1422, 1217, 756	0.13 <sup>4</sup>
75b	H	CH <sub>2</sub> Ph	H	H	10	46	oil	-60.4 (1.0, MeOH, 25)	C	1722, 1620, 1420, 1215, 755	0.13 <sup>4</sup>
76	H	CH <sub>2</sub> CH <sub>2</sub> Ph	H	H	10	84	oil	-61.2 (1.3, MeOH, 24)	C	1735, 1630, 1615, 1420, 1242, 1172, 1043, 702	0.66

Table-continued

Compd. No.	T <sup>4</sup>	T <sup>5</sup>	T <sup>6</sup>	T <sup>7</sup>	Method of prepn. (Examp. No.)	Yield (%)	mp (C°) (recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		R <sub>f</sub> <sup>a,2</sup> value (SiO <sub>2</sub> )
									Sampling <sup>a,1</sup> method	cm <sup>-1</sup>	
77		H	COPh	Et	15	36	oil	-46.2 (0.8, MeOH, 30)	C	1733, 1678, 1632, 1610, 1447, 1258, 1187, 1025, 1001, 751	0.32 <sup>3</sup>
78		H	CH <sub>2</sub> CH <sub>2</sub> Ph	H	15	46	oil	-48.4 (1.1, MeOH, 26)	C	1730, 1610, 1450, 1240, 1190, 750, 703	0.72 <sup>5</sup>
79		CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> Ph	H	15	62	amorph.	-82.2 (1.2, MeOH, 23)	A	1740, 1720, 1610, 1455, 1438, 1185, 748, 700	0.38
80		H	COCH <sub>3</sub>	Et	15	45	oil	-49.6 (0.9, MeOH, 30)	C	1736, 1597, 1398, 1378, 1333, 1250, 1191, 1047, 860, 752	0.29 <sup>3</sup>

<sup>a</sup> a and b represent diastereoisomers of the compound.

<sup>1</sup> A: KBr disk, C: neat.

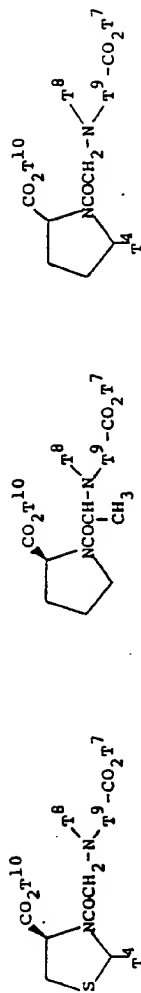
<sup>2</sup> EtOAc-CHCl<sub>3</sub>-AcOH (10:5:3).

<sup>3</sup> Benzene-EtOAc-AcOH (14:14:2:1).

<sup>4</sup> Benzene-EtOAc-AcOH (25:25:1).

<sup>5</sup> CHCl<sub>3</sub>-EtOH-AcOH (10:2:1)

Table V



Compound No. 81-85

Compound No. 86-98, 100-102

Compd. No.	T <sup>4</sup>	T <sup>7</sup>	T <sup>8</sup>	T <sup>9</sup>	T <sup>10</sup>	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf value (SiO <sub>2</sub> )
										Sampling method	cm <sup>-1</sup>	
81		H	H	-CH <sub>2</sub> -	H	11	48.2	181-182 (dec.) (H <sub>2</sub> O)	+271.2 (0.5, N NaOH, 24)	A	1400, 1200, 1740, 1672, 1560, 1440, 1380, 1335, 1210, 752	0.25 <sup>2</sup>
82		H	H	-CH <sub>2</sub> -	H	11	32.8	150-155 (H <sub>2</sub> O)	+94.7 (0.5, N NaOH, 23)	B	3420, 3210, 1650, 1240, 839, 790	0.45 <sup>3</sup>
83		H	H		H	11	44.8	150-153 (dec.) (EtOH-ether)	+86.5 (0.4, MeOH, 26)	A	3370-2900, 1655, 1602, 1175	0.74 <sup>4</sup>
84		H	H		H	11	50.3	172-173 (dec.) (EtOAc)	+78.9 (0.8, MeOH, 25)	A	3350, 1720, 1670, 1644, 1236, 744	0.65 <sup>4</sup>
85		H	H		H	11	27.2	174-175 (dec.) (H <sub>2</sub> O)		A	3400, 1720, 1660, 1610, 1492, 1452, 1240, 752, 700	0.21 <sup>5</sup>
86	H	Et	CH <sub>2</sub> CO <sub>2</sub> Et	-CH <sub>2</sub> -	H	13	quant.	oil	-52.2 (1.1, MeOH, 24)	C	1742, 1640, 1442, 1190, 1130, 752	0.21 <sup>5</sup>

Table-continued




Compd. No.	T <sup>4</sup> T <sup>7</sup> T <sup>8</sup>			T <sup>9</sup>	T <sup>10</sup>	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		Rf value (SiO <sub>2</sub> )
										Sampling method	cm <sup>-1</sup>	
87	H	H	CH <sub>2</sub> CO <sub>2</sub> H	-CH <sub>2</sub> -	H	7	26	amorph.	-32.8 (1.0, MeOH, 24)	B	3400, 1720, 1640, 1460, 1380	0.10 <sup>2</sup>
88	H	Et	CH <sub>2</sub> CO <sub>2</sub> Et	-CH <sub>2</sub> -	CH <sub>2</sub> Ph	12	45.2	oil	-67.9 (1.2, MeOH, 24)	C	3460, 1742, 1642, 1428, 1180	0.70 <sup>5</sup>
89a	H	H	H		H	16	33	216-218 (dec.) (H <sub>2</sub> O)	-141.1 (0.3, MeOH, 23)	B	2600, 1743, 1550, 1250, 1230, 800	0.20 <sup>6</sup>
89b	H	H	H		H	16	45	218-226 (dec.) (H <sub>2</sub> O)	+1.5 (0.5, MeOH, 23)	B	3310, 1610, 1575, 1160, 742	0.20 <sup>6</sup>
90	H	Et	COCH <sub>2</sub> Ph	-CH <sub>2</sub> -	CH <sub>2</sub> Ph	14	89	110-110.5 (benzene- <i>n</i> -hexane)	-114.0 (1.0, MeOH, 24)	A	3460, 1739, 1635, 1436, 1200, 1166	0.45 <sup>7</sup>
91	H	Et	COCH <sub>2</sub> Ph	-CH <sub>2</sub> -	H	13	quant.	oil	-99.7 (1.1, MeOH, 23)	D	1743, 1640, 1445, 1187	0.35 <sup>5</sup>
92	H	H	COCH <sub>2</sub> Ph	-CH <sub>2</sub> -	H	7	83	205-206 (EtOAc-MeOH)	-123.5 (1.0, MeOH, 24)	A	3430, 1727, 1635, 1598, 1426, 1184	0.38 <sup>8</sup>
93	H	Et	CO(CH <sub>2</sub> ) <sub>2</sub> Ph	-CH <sub>2</sub> -	CH <sub>2</sub> Ph	14	93	oil	-93.2 (1.0, MeOH, 24)	C	1746, 1655, 1647, 1447, 1188	0.51 <sup>7</sup>
94	H	Et	CO(CH <sub>2</sub> ) <sub>2</sub> Ph	-CH <sub>2</sub> -	H	13	quant.	oil	-94.7 (1.2, MeOH, 23)	D	1746, 1642, 1449, 1190	0.38 <sup>5</sup>
95	H	H	CO(CH <sub>2</sub> ) <sub>2</sub> Ph	-CH <sub>2</sub> -	H	7	96	amorph.	-104.3 (1.0, MeOH, 24)	A	3440, 1735, 1610, 1450, 1185	0.45 <sup>8</sup>
96	H	Et	CH <sub>2</sub> Ph	-CH <sub>2</sub> -	CH <sub>2</sub> Ph	12	46	oil	-66.0 (1.2, MeOH, 25)	D	1740, 1639, 1450, 1425, 1185	0.57 <sup>7</sup>
97	H	H	CH <sub>2</sub> Ph	-CH <sub>2</sub> -	H	7	87	amorph.	-59.0 (1.1, MeOH, 25)	A	3420, 1720, 1638, 1448, 1385	0.17 <sup>2</sup>
98	H	H	COCH <sub>3</sub> -CH <sub>2</sub> CO <sub>2</sub> H		CH <sub>2</sub> Ph -CH <sub>2</sub> CO <sub>2</sub> H	14	62	195-196 (dec.) (EtOAc)		B	1758, 1720, 1615, 1600, 1380, 750, 700	

Table-continued

Compd. <sup>†</sup> No.	T <sup>7</sup>	T <sup>8</sup>	T <sup>10</sup>	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] <sub>D</sub> deg. (c, solv., °C)	IR spectrum		R <sub>f</sub> value (SiO <sub>2</sub> )
								Sampling <sup>1</sup> method	cm <sup>-1</sup>	
99 <sup>11</sup>		H	CH <sub>2</sub> CH <sub>2</sub> Ph -CHCO <sub>2</sub> H	H	16	24	amorph.	B	3425, 1735, 1625, 1588	0.6 <sup>12</sup>
100	H	Et	CH <sub>2</sub> Ph	14	37	oil	-46.9 (0.5, MeOH, 23)	C	1740, 1642, 1453, 1425, 1170, 740	0.20 <sup>9</sup>
101	H	Et	H	13	90	oil	-35.9 (0.5, MeOH, 23)			0.25 <sup>2</sup>
102	H	H	H	7	90	228-230 (dec.) (MeOH)	-33.9 (0.4, MeOH, 23)	B	3450, 1720, 1610, 1305, 1228, 1200, 680	0.14 <sup>10</sup>

<sup>†</sup> a and b represent diastereoisomers of the compound.

<sup>1</sup> A: KBr disk, B: nujol mull, C: Neat, D: liquid cell (CHCl<sub>3</sub>).

<sup>2</sup> n-BuOH-AcOH-H<sub>2</sub>O (4:2:1).

<sup>3</sup> n-BuOH-AcOH-H<sub>2</sub>O (4:1:2).

<sup>4</sup> EtOH-CHCl<sub>3</sub>-AcOH (10:5:3).

<sup>5</sup> EtOH-EtOH-AcOH (40:1:1).

<sup>6</sup> EtOH-CHCl<sub>3</sub>-AcOH (7:5:1).

<sup>7</sup> Benzene-EtOH-AcOH (25:25:1).

<sup>8</sup> CHCl<sub>3</sub>-EtOH-AcOH (10:2:1).

<sup>9</sup> EtOH<sup>2</sup>

<sup>10</sup> n-Propanol-28% aq. NH<sub>3</sub> (7:3).

<sup>11</sup> Starting material: 1-(chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidinedicarboxylic acid; mp 204-206°C (dec.), [α]<sub>D</sub><sup>24</sup> +24.5° (c=1.2, MeOH), IR (nujol, cm<sup>-1</sup>) 3370, 1698, 1645, 1610, 1595, 1238, 758.

1 PHARMACOLOGICAL TEST 1

It has been known that aldose reductase participates in diabetic cataract which is one of the diabetic complications and that appearance is retarded or depressed by inhibition of the aldose reductase [Acta Societatis Ophthalmologicae Japonicae, 80, 1362 (1976)].  
5 The following method is used for the present test.

## (Method)

10 Aldose reductase is purified from rat lenses according to the method of Hoyman et al. [J. Biol. Chem., 240, 877 (1965)]. Action of the compounds (I) of this invention is evaluated by measurement of optical density according to the J.H. Kinoshita's method [Invest. Ophthal., 13, 713 (1974)].  
15 The reaction mixture for the measurement of the aldose reductase activity is 3.0ml [0.007M phosphate buffer solution (pH 6.2), 0.46M lithium sulfate,  $5 \times 10^{-5}$ M NADPH,  $4 \times 10^{-4}$ M DL glyceraldehyde, 10U aldose reductase,  $10^{-4}$  to  $10^{-10}$ M the compounds (I)]  
20 as total volume, and the absorbance thereof is measured at 340nm.

## (Result)

Table VI shows that the compounds (I) of this invention have a strong aldose reductase inhibition effect.  
25

1 Table VI. Inhibitory Activity of the Thiazolidine  
Compounds against Aldose Reductase

5	Compd. No.	IC <sub>50</sub> (M) *1
	22	8.2 x 10 <sup>-10</sup>
	23	1.1 x 10 <sup>-8</sup>
	47	1.6 x 10 <sup>-10</sup>
	56	1.7 x 10 <sup>-9</sup>
10	57	5.4 x 10 <sup>-9</sup>
	Control *2	1.0 x 10 <sup>-7</sup>

\*1 Molar concentration of a compound producing  
50% inhibition of aldose reductase.

15 \*2 Quercitrin: referred to Acta Societatis  
Ophthalmologicae Japonicae, 80, 1369-1370 (1976).

#### PHARMACOLOGICAL TEST 2

As the method of measurement of angiotensin I-  
20 converting enzyme activity, bioassay for the contractile  
response of isolated smooth muscle or the pressor re-  
sponse of normal animals and biochemical assay for the  
enzyme isolated from lung or other organs of animals  
are known. The former is found more advantageous than  
25 the latter for the examination of the conversion of  
angiotensin I to angiotensin II in vivo.

1        In the present study, therefore, we adopted the  
      bioassay for contractile response of isolated guinea  
      pig ileum to angiotensin I.

5        (Method)

      Isolated guinea pig ileum was suspended in the or-  
      gan bath containing 20ml of Tyrode's solution of 30°C  
      gassed with 95% O<sub>2</sub> + 5% CO<sub>2</sub>. The contraction induced  
      by the addition of angiotensin I (0.1µg/ml) at intervals  
10    of 10 minutes was recorded on a recticorder (Nihon Koden)  
      for 90 seconds using FD pick up (ST-1T-H, Nihon Koden)

      The test compounds were added to the bath 5 minutes  
      before the addition of angiotensin I.

      The inhibitory activity of angiotensin I-convert-  
15    ing enzyme was calculated by the following formula.

$$\frac{A - B}{A} \times 100$$

A: contractile intensity of angiotensin I  
      before addition of the compound

20    B: contractile intensity of angiotensin I  
      after addition of the compound

      From the fact that kininase II, which destroys  
      bradykinin having contractive action on isolated guinea  
      pig ileum, is thought to be identical with angiotensin  
      I-converting enzyme augmentation of the contractile  
25    response to bradykinin by test compounds was examined

- 1 by using bradykinin (0.005 $\mu$ g/ml) in place of angiotensin  
I according to the above mentioned method.

(Result)

- Concentration of a number of the compounds of this  
5 invention, which produced 50% inhibition of angiotensin  
I activity or augmentation of bradykinin activity in-  
ducing the contraction of guinea pig ileum, fell in the  
range of  $10^{-7}$  -  $10^{-9}$  M.

10 PHARMACOLOGICAL TEST 3

- The activity of angiotensin I-converting enzyme  
was measured by spectrophotometry according to the method  
of D.W. Cushman and H.S. Cheung [Biochem. Pharmacol.,  
20, 1637 (1971)]. That is, the absorbance of hippuric  
15 acid was measured, which is liberated by incubating  
hippuryl-L-histidyl-L-leucine (HHL) as substrate in the  
presence of angiotensin I-converting enzyme extracted  
from rabbit lung.

20 (Method)

The reaction mixture is as follows:

- 100mM phosphate buffer (pH 8.3)  
300mM sodium chloride  
5mM HHL  
25  $10^{-3}$  -  $10^{-9}$  M enzyme inhibitor  
5mU enzyme

1           0.25ml of the above mixture was incubated at 37°C  
for 30 minutes and the reaction was stopped by adding  
0.25ml of 1 N hydrochloric acid. To this solution,  
1.5ml of ethyl acetate was added in order to extract  
5   hippuric acid. 1.0ml of ethyl acetate layer was col-  
lected and evaporated to dryness, and the residue ob-  
tained was dissolved in 1.0ml of water. The absorbance  
of this solution was measured at 228nm.

The inhibitory activity of angiotensin I-converting  
10 enzyme was calculated by the following formula:

$$\text{Percent inhibition} = \frac{A - B}{A} \times 100$$

A: absorbance of reaction solution before  
addition of the compound

B: absorbance of reaction solution after  
15 addition of the compound

Concentration of compound producing 50% inhibition of  
angiotensin I-converting enzyme ( $IC_{50}$ )

The solution containing compounds at the concentra-  
20 tion of  $1 \times 10^{-3}M$  to  $1 \times 10^{-9}M$  was incubated and percent  
inhibition at each concentration was calculated accord-  
ing to the above formula, and then  $IC_{50}$ , concentration  
of the compound producing 50% inhibition of the enzyme  
activity, was determined.

25 (Result)

$IC_{50}$  of a number of the compounds of this invention,

- 1 fell in the range of  $10^{-7}$  -  $10^{-10}$  M.

#### TOXICITY TEST

- The acute toxicity of compounds 47 and 56 is 1000 -  
5 1500mg/kg.

#### (Experimental animals)

- The male ddy-std. strain mice (4 weeks of age,  
weighing 19-21g) were placed in a breeding room of con-  
10 stant temperature and humidity ( $23 \pm 1^\circ\text{C}$ ,  $55 \pm 5\%$ ) and fed  
freely pellet diet (CE-2, Clea Japan, Inc.) and water  
ad. libitum for a week. The mice showing the normal  
growth were selected for the experiment.

- 15 (Method of administration)

Test compounds are dissolved in distilled water and  
administered (i.v.) in a dose of 0.5ml/20g body weight.

- It is found in the above pharmacological and  
toxicity test that the compounds (I) of this invention  
20 are useful as drugs for therapy or prophylaxis of the  
diabetic complications and as antihypertensive agents.

- In case the compounds are used for preventing or  
relieving diabetic complications, the dosage forms are  
tablet, capsule, granule, powder, suppository, injection,  
25 ophthalmic solution, ophthalmic ointment, etc. These  
preparations can also contain general excipients.

1           On the other hand, in case the compounds are used  
 for reducing blood pressure, they can be given with the  
 combination of diuretics such as probenecid, carinamide,  
 hydroflumethiazide, furosemide, and bumetanide same as  
 5   other antihypertensive agents. The compounds can be  
 administered either orally or parenterally. The dosage  
 forms are tablet, capsule, granule, powder, suppository,  
 injection, etc. In the treatment of hypertension, these  
 preparations can contain not only general excipients  
 10 but also other antihypertensive agents such as reserpine,  
 $\alpha$ -methyldopa, guanethidine, clonidine, hydralazine, etc.,  
 or  $\beta$ -adrenergic blocking agents such as propranolol,  
 alprenolol, pindolol, bufetolol, bupranolol, bunitrolol,  
 practolol, oxprenolol, indenolol, timolol, bunolol, etc.  
 15           The dose is adjusted depending on symptom, dosage  
 form, etc. But, usual daily dosage is 1 to 5000mg, pref-  
 erably 10 to 1000mg, in one or a few divided doses.

#### EXAMPLES OF FORMULATION

##### 20   (1) Oral drug

##### (a) tablet

	compound 13	50mg
	lactose	120mg
	crystalline cellulose	60mg
25	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
<hr/>		
	Total	240mg

1	compound 22	100mg
	lactose	95mg
	crystalline cellulose	45mg
	calcium carboxymethylcellulose	7mg
5	magnesium stearate	3mg
	<hr/>	
	Total	240mg
	compound 23	150mg
	lactose	60mg
10	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
	<hr/>	
	Total	250mg
15	compound 56	150mg
	lactose	60mg
	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
20	magnesium stearate	3mg
	<hr/>	
	Total	250mg
	compound 74	150mg
	lactose	60mg
25	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg

1	magnesium stearate	3mg,
	Total	250mg
	compound 88	150mg
5	lactose	60mg
	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
	Total	250mg

The tablets may be treated with common film-coating and further with sugar-coating.

	(b) granule	
15	compound 13	30mg
	polyvinylpyrrolidone	25mg
	lactose	385mg
	hydroxypropylcellulose	50mg
20	talc	10mg
	Total	500mg
	compound 22	30mg
	polyvinylpyrrolidone	25mg
25	lactose	385mg
	hydroxypropylcellulose	50mg

1	talc	10mg.
	Total	500mg
5	compound 94	30mg
	polyvinylpyrrolidone	25mg
	lactose	385mg
	hydroxypropylcellulose	50mg
	talc	10mg
10	Total	500mg
	(c) powder	
	compound 13	250mg
	lactose	240mg
15	starch	480mg
	colloidal silica	30mg
	Total	1000mg
20	compound 65	300mg
	lactose	230mg
	starch	440mg
	colloidal silica	30mg
	Total	1000mg
25	compound 79	300mg
	lactose	230mg

1	starch	440mg
	colloidal silica	30mg
	Total	1000mg
5	compound 100	300mg
	lactose	230mg
	starch	440mg
	colloidal silica	30mg
	Total	1000mg
10	(d) capsule	
	compound 13	50mg
	lactose	102mg
	crystalline cellulose	36mg
15	colloidal silica	2mg
	Total	190mg
	compound 23	100mg
20	lactose	52mg
	crystalline cellulose	36mg
	colloidal silica	2mg
	Total	190mg
25	compound 74	200mg
	glycerin	179.98mg

1	butyl p-hydroxybenzoate	0.02mg
	Total	380mg

5	compound 81	30mg
	glycerin	349.98mg
	butyl p-hydroxybenzoate	0.02mg
	Total	380mg

10	compound 98	200mg
	glycerin	179.98mg
	butyl p-hydroxybenzoate	0.02mg
	Total	380mg

15 (2) Injection

(a) 1 to 30mg of compound 98 is contained in 1ml of the aqueous solution (pH 6.5-7.0).

20 (b) 1 to 30mg of compound 73 is contained in 1ml of the aqueous solution (pH 6.5-7.0).

(3) Ophthalmic solution

The following composition is contained in 5ml of the aqueous solution (pH 6.0).

25

Compound 23

50mg

1           propyl p-hydroxybenzoate           0.7mg  
          methyl p-hydroxybenzoate           1.3mg  
          sodium hydroxide           proper quantity

5   (4) Ophthalmic ointment

The following composition is contained in 1g.

          compound 22                           20mg  
          white petrolatum                   889.8mg  
10       mineral oil                           100mg  
          butyl p-hydroxybenzoate           0.2mg

(5) Suppository

The following composition is contained in 1g.

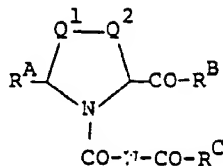
15           compound 47                           50mg  
          polyethylen glycol 1000           800mg  
          polyethylen glycol 4000           150mg  
20

1 CLAIMS

0031104

1. A compound of the formula [I]

5



[I]

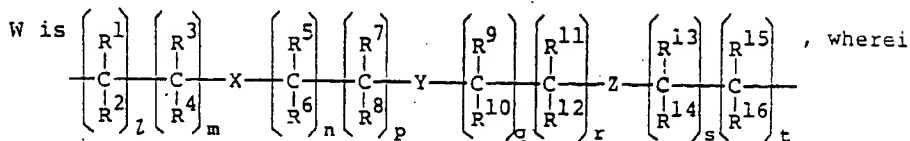
wherein

10  $Q^1$  and  $Q^2$  each is methylene or sulfur, but  $Q^1$  and  $Q^2$  are not sulfur at the same time;

$R^A$  is  $R^a$  or  $R^b$ ;

$R^B$  and  $R^C$  each is  $R^c$ ;

15



X, Y and Z each is single bond,  $-CH_2-$ ,  $-C \equiv C-$ ,  $-C=C-$ ,  $-O-$ ,  $-CO-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-C(=O)-$ ,  $-NHCONH-$ ,  $-N \text{ (cyclohexane ring) } -$  or  $-N(R^{21})-$ ;

20

$l, m, n, p, q, r, s$  and  $t$  each is 0, 1, 2 or 3;  
 $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$  and  $R^{21}$  each is  $R^d$ ;

$R^A$  is  $R^b$  when W is  $-CH-NH-C(=O)-$  or  $-CH-CH_2-$ , wherein  $R^{22}, R^{23}, R^{24}, R^{25}$  and  $R^{26}$  each is  $R^d$ ;

25

$R^a$  is selected from the group consisting of

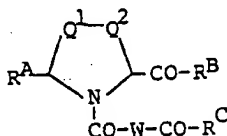
- (i) hydrogen, lower alkyl and lower alkenyl, and
- (ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl,

1 TITLE OF INVENTION

THIAZOLIDINE AND PYRROLIDINE COMPOUNDS, PROCESSES FOR THEIR  
 PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING  
 5 THEM

BACKGROUND OF INVENTION

This invention relates to thiazolidine and pyrrolidine  
 10 compounds of the general formula



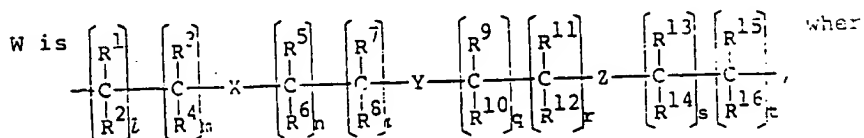
[I],

wherein

$\text{Q}^1$  and  $\text{Q}^2$  each is methylene or sulfur, but  $\text{Q}^1$  and  $\text{Q}^2$   
 are not sulfur at the same time;

$\text{R}^A$  is  $\text{R}^a$  or  $\text{R}^b$ ;

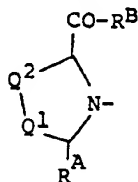
$\text{R}^B$  and  $\text{R}^C$  each is  $\text{R}^C$ ;



25 X, Y and Z each is single bond,  $-\text{CH}_2-$ ,  $-\text{C}=\text{C}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{C}_6\text{H}_4-$

- 1  $R^C$  is selected from the group consisting of  
 (a) (i) hydroxy, lower alkoxy and amino, and  
 (ii) lower alkoxy and amino substituted by at least one substituent  
 selected from the group consisting of lower alkyl, aralkyl,  
 heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy,  
 5 aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy,  
 aryl, heteroaryl, substituted aralkyl and substituted aryl  
 wherein the substituent is lower alkyl, lower alkoxy, halogen  
 or amino;

- (b) (i) aryloxy and heteroaryloxy, and  
 (ii) aryloxy and heteroaryloxy substituted by at least one  
 10 substituent selected from the group consisting of lower alkyl,  
 hydroxy, lower alkoxy, halogen and amino, and  
 (c)



- 15  $R^d$  is selected from the group consisting of  
 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-  
 aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,  
 carboxy, amino, mercapto and sulfo, and  
 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl,  
 arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino,  
 mercapto and sulfo substituted by at least one substituent  
 20 selected from the group consisting of lower alkyl, lower alkenyl,  
 lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy,  
 aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino,  
 acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro,  
 cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio  
 and lower alkylsulfinyl;  
 25 (b) (i) phenyl and naphthyl, and  
 (ii) phenyl and naphthyl substituted by at least one substituent

1 aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-carbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and

10 (ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-carbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, 15 lower alkylaminosulfonyl and lower alkylsulfinyl;

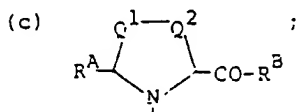
$R^C$  is selected from the group consisting of

(a)(i) hydroxy, lower alkoxy and amino, and

(ii) lower alkoxy, and amino substituted by at least one substituent selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, 20 lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, hetero-aryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen or amino;

(b)(i) aryloxy and heteroaryloxy, and

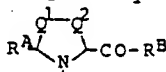
25 (ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and



- 1 aminophenyl, 4-acetaminophenyl, 4-[(benzyloxycarbonyl)amino]phenyl,  
 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxy-  
 phenyl, 4-hydroxyphenyl, 3-benzoxypyphenyl, 4-(benzyloxycarbonyloxy)-  
 phenyl, 3,4-dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxy-  
 phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxy-  
 5 phenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-4-methoxyphenyl,  
 4-hydroxy-3-methoxyphenyl, 3,4-methyleneedioxyphenyl, 2-cyano-  
 phenyl, 3-cyanophenyl, 4-cyanophenyl, 2-nitrosophenyl, 3-  
 nitrosophenyl, 4-nitrosophenyl, 2-hydroxy-5-sulfamoylphenyl,  
 2-hydroxy-5-[(dipropylamino)sulfonyl]phenyl, 3-(methylsulfinyl)phenyl,  
 3-(difluoromethoxy)phenyl, 1-naphthyl, 2-furyl, 2-(5-methyl)furyl,  
 2-thienyl, 3-pyridyl or 4-pyridyl.

0

5. A compound of claim 1 wherein R<sup>C</sup> is hydroxy, methoxy, ethoxy, butoxy, amino, hydroxyamino, succinimidomethoxy, 1-succinimidoethoxy, phthalimidomethoxy, 2-phthalimidoethoxy, pivaloyloxymethoxy, 1-pivaloyloxyethoxy, benzyloxy, phenoxy, benzyloxyamino or

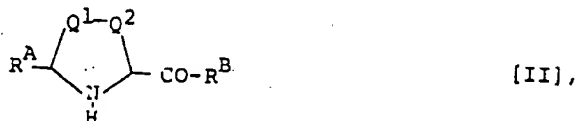


5

6. A compound of claim 1 wherein R<sup>d</sup> is hydrogen, methyl, ethyl, propyl, 1-methylethyl, 2-methylpropyl, 4-methylpentyl, vinyl, allyl, 2-butenyl, 1,3-butanediethyl, 1-methylvinyl, hydroxymethyl, carboxymethyl, 2-carboxyethyl, cyclohexyl, cyclohexylmethyl, benzyl, 2-phenylethyl, 3-phenylbutyl, 2-(1-naphthyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(3,4-dichlorophenyl)ethyl, 4-methoxybenzyl, 2-(4-methoxyphenyl)ethyl, 4-hydroxybenzyl, 2-(4-hydroxyphenyl)ethyl, (2-pyridyl)methyl, (4-pyridyl)methyl, 2-(2-pyridyl)ethyl, 2-(4-pyridyl)ethyl, (4-imidazolyl)methyl, 3-indolylmethyl, 2-(methylthio)ethyl, 4-aminobutyl, 5-aminopentyl, 4-guanidinobutyl, 4-(aminomethyl)benzyl, phenoxy-methyl, (phenylthio)methyl, 1-amino-2-phenylethyl, 1-amino-3-methylbutyl phenyl, naphthyl, 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethylaminophenyl, 4-acetaminophenyl, 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-benzoxypyphenyl, 3,4-

1. The compounds [I] of this invention can be prepared by following process.

(i) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II]



wherein  $\text{R}^{\text{A}}$  and  $\text{R}^{\text{B}}$  may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when  $\text{R}^{\text{A}}$  and  $\text{R}^{\text{B}}$  include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), with the reactive derivative of carboxylic acid of the formula [III] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, lactone, etc.) by general methods used in peptide syntheses or amide formation reactions



wherein W and  $\text{R}^{\text{C}}$  may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when W and  $\text{R}^{\text{C}}$  include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), followed by removal of protective groups by well-known methods (e.g., hydrolysis, hydrogenolysis, ammonolysis, alcoholysis, etc.).

This procedures of deprotection can be applied in the following methods.

1           10. A compound of claim 4 which is (4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid methyl ester].

5           11. A compound according to claim 4 which is (4R)-3-(11-carboxyundecanoyl)-2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid;

(4R,4'R)-3,3'-(~~dec~~ecanedioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid];

(4R,4'R)-3,3'-(~~dec~~ecanedioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid];

10          (4R)-3-(8-carboxyoctanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid;

(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid];

(4R)-3-(7-carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

15          12. A compound according to claim 4 which is (4R)-3-[[[1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid;

(4R)-3-[[[1-(ethoxycarbonyl)-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

20          13. A compound according to claim 4 which is 1-[[[1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid;

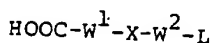
1-[[[1-(ethoxycarbonyl)-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid.

25          14. A compound of claim 4 which is (4R)-3-[[[1-carboxy-3-phenylpropyl)thio]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

15. A compound of claim 4 which is (4R)-3-(4-carboxybutanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

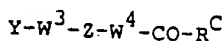
1° protected such as (i) above, in the presence of proper alkaline and/or organic bases, if necessary, by known methods.

(iii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [VII] (e.g.,  
5 mentioned in (i) above)



[VII]

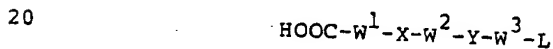
10 and then with a compound of the formula [VIII]



[VIII]

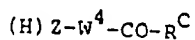
by the same method as (ii) above.

15 (iv) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IX] (e.g., mentioned in (i) above)



[IX],

and then with a compound of the formula [X]



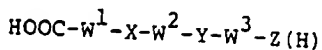
[X]

25 by the same method as (ii) above.

- 1         $R^a$  is selected from the group consisting of  
    (i) hydrogen, lower alkyl and lower alkenyl, and  
    (ii) lower alkyl and lower alkenyl substituted by at least one  
    substituent selected from the group consisting of lower alkyl,  
    lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,  
5      acyloxy, halogen, nitro, cyano, amino, lower alkylamino, di-  
    alkylamino, acylamino, mercapto, acylmercapto, lower alkylthio,  
    carboxy, lower alkoxy-carbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl,  
    sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

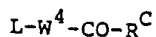
- $R^b$  is selected from the group consisting of  
    (a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and  
10     (ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl  
    substituted by at least one substituent selected from the group  
    consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl,  
    hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen,  
    nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino,  
    mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-  
    carbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl, sulfamoyl, lower  
15     alkylaminosulfonyl and lower alkylsulfinyl, and  
    (iii) carboxy, lower alkoxy-carbonyl, aralkyloxy-carbonyl, aryloxy-  
    carbonyl and heteroaryloxy-carbonyl;  
    (b) (i) phenyl and naphthyl, and  
    (ii) phenyl and naphthyl substituted by at least one substituent  
    selected from the group consisting of lower alkyl, lower alkenyl,  
20     halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,  
    aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino,  
    lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto,  
    lower alkylthio, carboxy, lower alkoxy-carbonyl, aralkyloxy-carbonyl,  
    aryloxy-carbonyl, sulfamoyl, lower alkylaminosulfonyl and lower  
    alkylsulfinyl;  
    (c) (i) furyl, thienyl and pyridyl, and  
25     (ii) furyl, thienyl and pyridyl substituted by at least one  
    substituent selected from the group consisting of lower alkyl,

1 reactive derivative of carboxylic acid of the formula [XV]  
 (e.g., mentioned in (v) above)



[XV],

5 and then with a compound of the formula [XVI]



[XVI]

10 by the same method as (ii) above.

(viii) A compound of the formula [I] is also yielded  
 by converting a compound of the formula [I] prepared by  
 any method above-mentioned by well-known methods (e.g.,  
 oxidation, formation of oxime, hydrazone and semicarbazone,  
 15 addition to double bond, etc.)

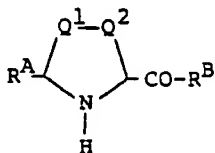
The compounds [I] of this invention are effective on  
 preventing or relieving diabetic complications.

In diabetic patients, high levels of hexoses (e.g.,  
 20 glucose, galactose, etc.) in blood lead to the accumulation  
 of sugar alcohols (e.g., sorbitol, galactitol, etc.) in  
 tissues. It is known that this accumulation causes the  
 swelling of cells to induce complications of diabetic  
 cataract, diabetic retinopathy, diabetic nephropathy, diabetic  
 25 neuropathy, etc. [R. Quan-Ma et al., Biochem. Biophys. Res.  
 Comm., 22, 492 (1966)]. For example, R. Gitzelman et al.

- 1 acylamino, acylmercapto, lower alkoxy carbonyl, sulfo, halogen,  
 nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkyl-  
 thio and lower alkylsulfinyl;
- (b) (i) phenyl and naphthyl, and  
 (ii) phenyl and naphthyl substituted by at least one substituent  
 5 selected from the group consisting of lower alkyl, lower alkoxy,  
 lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro,  
 cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl,  
 halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxy carbonyl,  
 sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;
- (c) (i) furyl, thienyl and pyridyl, and  
 10 (ii) furyl, thienyl and pyridyl substituted by at least one  
 substituent selected from the group consisting of lower alkyl,  
 lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,  
 halogen, nitro, cyano, acylamino, mercapto, acylmercapto,  
 halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-  
 dioxy, lower alkoxy carbonyl, sulfo, sulfamoyl, lower alkyl-  
 aminosulfonyl and lower alkylsulfinyl;
- 15 and salts thereof

which comprises

- (i) reacting a compound of the formula [II]



[II]

- 25 wherein  $R^A$  and  $R^B$  may include suitable protection of any reactive  
 groups with the reactive derivative of a carboxylic acid of the  
 formula [III] (e.g., acyl halide, acid anhydride, mixed anhydride,  
 active ester, etc.)

1 salts to be generally used as medicine such as sodium salt,  
potassium salt, calcium salt, magnesium salt, aluminum salt,  
ammonium salt, diethylamine salt, triethanolamine, etc.

5 The compounds of formula [I] have the stereoisomers  
which are within the limit of this invention, because they  
have one or more asymmetric carbon atoms.

Typical examples are shown below, although this invention  
is not limited to these examples.

10

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20

25

1 of any reactive groups, followed by removal of protective  
groups, if necessary, to yield a compound of the formula [I];

(iii) reacting a compound of the formula [II] with the  
reactive derivative of carboxylic acid of the formula [VII]

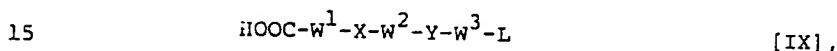


and then with a compound of the formula [VIII]



10 by the same method as (ii) above to yield a compound of the  
formula [I];

(iv) reacting a compound of the formula [II] with the  
reactive derivative of carboxylic acid of the formula [IX]



and then with a compound of the formula [X]



20 by the same method as (ii) above to yield a compound of  
the formula [I];

(v) reacting a compound of the formula [II] with the  
reactive derivative of carboxylic acid of the formula [XI]



25 and then with a compound of the formula [XII]

- 1 pyrrolidine ring. The same shall be applied hereinaft,
- \*2 Two spots were observed on the TLC (ethyl acetate-chloroform-acetic acid (10:5:3)), and two products could be separated by silica gel column chromatography
- 5 From NMR spectra, the upper and lower spots were identified as the titled compound and (4R,4R')-3,3'-(octanedioyl)bis[2-(2-hydroxyphenyl)-4-thiazolidine-carboxylic acid] (compound 40), respectively.
- \*3 Silica gel, ethyl acetate-chloroform-acetic acid
- 10 (10:5:3).

The compounds shown in Table I and III were prepared by the same procedure as described above.

The following compounds are also prepared by the same

15 procedure as EXAMPLE 1.

(4R)-3-carboxyacetyl-4-thiazolidinecarboxylic acid

(4R)-3-(3-carboxypropanoyl)-2-phenyl-4-thiazolidine-carboxylic acid

(4R)-3-[3-(2-carboxyethylsulfinyl)propanoyl]-2-(2-

20 hydroxyphenyl)-4-thiazolidinecarboxylic acid

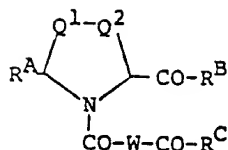
(4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxybutanoyl)-2-(3-hydroxyphenyl)-4-thiazolidinecarboxylic acid

25 (4R)-3-(5-carboxypentanoyl)-2-(4-methylphenyl)-4-thiazolidinecarboxylic acid

1

5



[I]

wherein

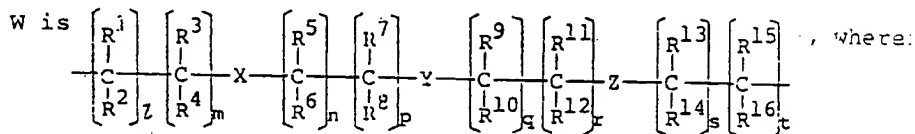
0

$\text{Q}^1$  and  $\text{Q}^2$  each is methylene or sulfur, but  $\text{Q}^1$  and  $\text{Q}^2$  are not sulfur at the same time;

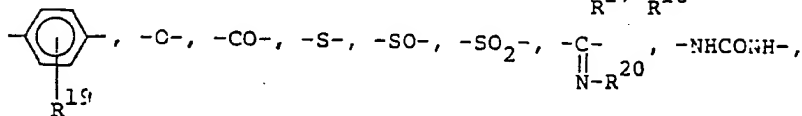
$\text{R}^{\text{A}}$  is  $\text{R}^{\text{a}}$  or  $\text{R}^{\text{b}}$ ;

$\text{R}^{\text{B}}$  and  $\text{R}^{\text{C}}$  each is  $\text{R}^{\text{c}}$ ;

5



X, Y and Z each is single bond,  $-\text{CH}_2-$ ,  $-\text{C}=\text{C}-$ ,  $-\text{C}\equiv\text{C}-$ ,



0

5

- 1           thiazolidinecarboxylic acid  
          (4R)-3-(6-carboxyhexanoyl)-2-(2-furyl)-4-thiazolidine-  
          carboxylic acid  
          (4R)-3-(7-carboxyheptanoyl)-2-(2-thienyl)-4-thiazolidine-  
5           carboxylic acid  
          (4R)-3-(8-carboxyoctanoyl)-2-(3-pyridyl)-4-thiazolidine-  
          carboxylic acid  
          (4R)-3-(9-carboxynonanoyl)-2-(1-naphthyl)-4-thiazolidine-  
          carboxylic acid  
10          (4R)-3-(5-carboxypentanoyl)-2-(2-hydroxy-4-sulfamoyl-  
          phenyl)-4-thiazolidinecarboxylic acid  
          (4R)-3-(6-carboxyhexanoyl)-2-(3-cyanophenyl)-4-  
          thiazolidinecarboxylic acid  
          (4R)-3-(7-carboxyheptanoyl)-2-(3-difluoromethoxyphenyl)-  
15          4-thiazolidinecarboxylic acid  
          (4R)-3-(8-carboxyoctanoyl)-2-(4-carboxyphenyl)-4-  
          thiazolidinecarboxylic acid  
          (4R)-3-(9-carboxynonanoyl)-2-(3-methylsulfinylphenyl)-4-  
20          thiazolidinecarboxylic acid

## EXAMPLE 2

(4R,4'R)-3,3'-(Octanedioyl)bis[2-(2-hydroxyphenyl)-4-  
thiazolidinecarboxylic acid (compound 40)]

- 25           To a stirred solution of (4R)-2-(2-hydroxyphenyl)-  
          4-thiazolidinecarboxylic acid (6.8g) in 1M  
          potassium carbonate (45ml), octanedioyl dichloride (3.2g)

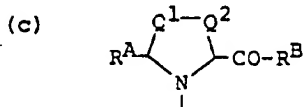
- 1 acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy carbonyl, aralkyloxy carbonyl, aryloxy carbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfanyl; (c) (i) furyl, thienyl and pyridyl, and (ii) furyl, thienyl and pyridyl substituted by at least one
- 5 substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy carbonyl, aralkyloxy carbonyl, aryloxy carbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfanyl;

10

$R^C$  is selected from the group consisting of

- (a) (i) hydroxy, lower alkoxy and amino, and (ii) lower alkoxy and amino substituted by at least one substituent selected from the group consisting of lower
- 15 alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen, or amino;

- (b) (i) aryloxy and heteroaryloxy, and (ii) aryloxy and heteroaryloxy substituted by at least one
- 20 substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and



$R^d$  is selected from the group consisting of

- 25 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and

1 organic layer was washed with saturated sodium chloride  
 solution, dried over anhydrous magnesium sulfate, and  
 evaporated in vacuo. The residual oil was purified by  
 silica gel column chromatography to give 7.6g (86%) of  
 5 the titled compound: mp 93-97°C (dec.);  $[\alpha]_D^{27} +123.6^\circ$   
 (c=0.5, methanol). IR (nujol,  $\text{cm}^{-1}$ ): 1720 (COOH), 1620  
 (CON), 1600 (aromatic), 1230, 1090, 855, 765. MNR ( $\text{CD}_3\text{OD}$ )  
 $\delta$ : 0.7-1.7 (8H, m,  $-\text{CH}_2(\text{CH}_2)_4-\text{CH}_2-$ ), 1.8-2.4 (4H, m,  
 $-\text{CH}_2(\text{CH}_2)_4-\text{CH}_2$ ), 3.25 (4H, d,  $J=7.5\text{Hz}$ ,  $\text{C}_5\text{-H}$ ), 4.81 (2H,  
 10 t,  $J=7.5\text{Hz}$ ,  $\text{C}_4\text{-H}$ ), 6.35 (2H, s,  $\text{C}_2\text{-H}$ ), 6.7-8.0 (8H, m,  
 arom. H). TLC: Rf value\* 0.34.

\* Silica gel, ethyl acetate-chloroform-acetic acid  
 (10:5:3).

15

The compounds shown in Table II and III were prepared by  
 the same procedure as described above.

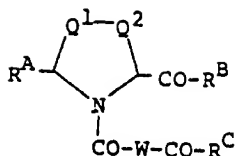
### EXAMPLE 3

20 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(3-cyanophenyl)-4-  
 thiazolidinecarboxylic acid] (compound 36)

To a stirred solution of (4R)-2-(3-cyanophenyl)-4-  
 thiazolidinecarboxylic acid (4.7g) in 1M sodium  
 25 carbonate (30ml), heptanedioyl dichloride (2.1g)  
 was added dropwise under ice-cooling. The reaction mixture  
 was stirred for 30 minutes at the same temperature, and

1

5



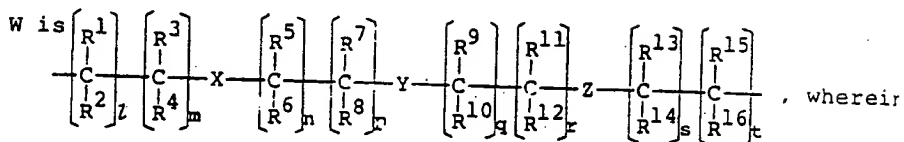
[I]

10 wherein

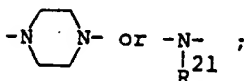
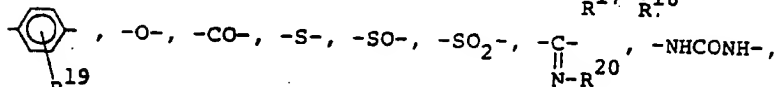
$\text{Q}^1$  and  $\text{Q}^2$  each is methylene or sulfur, but  $\text{Q}^1$  and  $\text{Q}^2$  are not sulfur at the same time;

$\text{R}^A$  is  $\text{R}^a$  or  $\text{R}^b$ ;

15  $\text{R}^B$  and  $\text{R}^C$  each is  $\text{R}^C$ ;

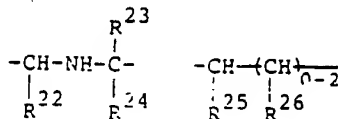


20 X, Y and Z each is single bond,  $-\text{CH}_2-$ ,  $-\text{C}(\text{R}^{17})=\text{C}(\text{R}^{18})-$ ,  $-\text{C}\equiv\text{C}-$ ,



25 l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;  
 $\text{R}^1, \text{R}^2, \text{R}^3, \dots, \text{R}^{20}$  and  $\text{R}^{21}$  each is  $\text{R}^d$ ;

$\text{R}^A$  is  $\text{R}^b$  when W is or , wherein  $\text{R}^{22}$ ,



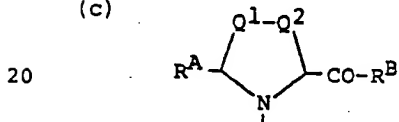
- 1 (4R,4'R)-3,3'-(pentanedioyl)bis[2-(3-hydroxyphenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(hexanedioyl)bis[2-(4-methylphenyl)-4-thiazolidinecarboxylic acid]
- 5 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(octanedioyl)bis[2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 10 (4R,4'R)-3,3'-(3,3'-thiodipropionyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 15 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(decanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 20 (4R,4'R)-3,3'-(4,4'-oxydibutanoyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(3,3'-sulfonyldipropionyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 25 (4R,4'R)-3,3'-(decanedioyl)bis[2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid]  
(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid]

- 1 (c)(i) furyl, thienyl and pyridyl, and  
 (ii) furyl, thienyl and pyridyl substituted by at least one  
 substituent selected from the group consisting of lower alkyl,  
 lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy,  
 halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen,  
 5 nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino,  
 mercapto, acylmercapto, lower alkylthio, carboxy, lower  
 alkoxy-carbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl, sulfamoyl,  
 lower alkylsulfonyl, and lower alkylsulfinyl;

$R^C$  is selected from the group consisting of

- (a)(i) hydroxy, lower alkoxy and amino, and  
 10 (ii) lower alkoxy and amino substituted by at least one  
 substituent selected from the group consisting of lower  
 alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl,  
 hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy,  
 heteroaryloxy, acyloxy, aryl, heteroaryl, substituted  
 aralkyl and substituted aryl wherein the substituent is  
 lower alkyl, lower alkoxy, halogen or amino;  
 15 (b)(i) aryloxy and heteroaryloxy, and  
 (ii) aryloxy and heteroaryloxy substituted by at least one  
 substituent selected from the group consisting of lower alkyl,  
 hydroxy, lower alkoxy, halogen and amino, and

(c)



$R^d$  is selected from the group consisting of

- (a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl,  
 heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl,  
 hydroxy, carboxy, amino, mercapto and sulfo, and  
 25 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,  
 alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,  
 carboxy, amino, mercapto and sulfo substituted by at least

1 reaction mixture was stirred for 1 hour at the same  
temperature, and the separated crystals were filtered to  
give 4.7g (69%) of the titled compound as disodium salt:  
mp 111-113°C (dec.) (water);  $[\alpha]_D^{25} +88.2^\circ$  (c=0.5, methanol)  
5 IR (nujol,  $\text{cm}^{-1}$ ): 1635 (CON), 1585 ( $\text{COO}^-$ ), 1520 and 1355  
( $\text{NO}_2$ ), 1095, 730. TLC: Rf value\* 0.28.

\* Silica gel, ethyl acetate-chloroform-acetic acid  
(10:5:3).

10

## EXAMPLE 5

(4R)-3-(3-Carboxypropanoyl)-2-(2-hydroxyphenyl)-4-  
thiazolidinecarboxylic acid (compound 6)

15 To a stirred solution of (4R)-2-(2-hydroxyphenyl)-  
4-thiazolidinecarboxylic acid (4.5g) and  
triethylamine (4.0g) in acetone (100ml),  
succinic anhydride (2.0g) was added at room  
temperature, and stirred for 3 hours at the same  
20 temperature. The reaction mixture was concentrated  
in vacuo, and acidified with dilute hydrochloric acid.  
The separated oil was extracted with ethyl acetate, and  
the organic layer was washed with saturated sodium chloride  
solution, dried over anhydrous magnesium sulfate, and  
25 evaporated in vacuo to give 4.9g (75%) of the titled  
compound: mp 190-191°C (dec.) (ethyl acetate-methanol);  
 $[\alpha]_D^{27} +181.6^\circ$  (c=1.0, methanol). IR (nujol,  $\text{cm}^{-1}$ ): 3210

24

1 After the addition, the reaction mixture was stirred for  
1.5 hours at the same temperature. After the filtration  
of solution, the filtrate was acidified with dilute  
hydrochloric acid, and extracted with ethyl acetate. The  
5 organic layer was washed with saturated sodium chloride  
solution, dried over anhydrous magnesium sulfate, and  
evaporated in vacuo. The residual oil was purified  
by silica gel column chromatography to give 7.8g (44%)  
of the titled compound:  $[\alpha]_D^{25} +161.6^\circ$  (c=1.0, methanol).  
10 IR (KBr,  $\text{cm}^{-1}$ ): 3380 (OH), 1723 (COOH, COOCH<sub>3</sub>), 1624  
(CON), 1235, 1200, 1174, 764.

The compounds shown in Table I and II were prepared by  
the same procedure as described above.

15

#### EXAMPLE 7

(4R)-3-(3-Carboxy-2-methylpropanoyl)-2-(2-hydroxyphenyl)-  
4-thiazolidinecarboxylic acid (compound 5)

20 (4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-  
(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound  
4) (7.1g) was dissolved in 2N sodium hydroxide (40ml)  
and stirred for 1 hour at room temperature. The  
resulting solution was acidified with dilute hydrochloric  
25 acid and the separated crystals were filtered to give  
5.1g (75%) of the titled compound: mp 163-164°C (dec.)



European Patent  
Office

# EUROPEAN SEARCH REPORT

0031104

Application number

EP 80 10 7869

-2-

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P	<u>FR - A - 2 445 324</u> (SANTEN PHARM) *"Revendications"* --	1-5	
P	<u>FR - A - 2 440 365</u> (SANTEN PHARM) *"Revendications"* --	1-5	
P	<u>FR - A - 2 434 150</u> (YOSHITOMI PHARM.) *"Revendications"* ----	1-5	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)



European Patent  
Office

# EUROPEAN SEARCH REPORT

0031104

Application number

EP 80 10 7869

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
*	<u>US - A - 4 154 937</u> (D.W. CUSHMAN et al. ) * Columns 1-2 * --	1-3, 5, 6, 7, 16	C 07 D 277/06 207/16 A 61 K 31/425 31/40
*	<u>GB - A - 2 000 508</u> (YOSHITOMI PHARM. LTD.) * Pages 1-2 * --	1-5, 7, 16	
	<u>FR - A - 2 407 204</u> (SANDOZ S.A.) * "Revendications" * --	1-5	
	<u>FR - A - 2 412 537</u> (SCIENCE UNION ET CIE) * "Revendications" * --	1, 2	TECHNICAL FIELDS SEARCHED (Int. Cl.) C 07 D 277/06 277/16
	<u>FR - A - 2 340 933</u> (E.R. SQUIBB AND SONS) * "Revendications" * --	1-3, 5-7	CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
	<u>FR - A - 2 340 932</u> (E.R. SQUIBB AND SONS) * "Revendications" * --	1-3, 5-7	
	<u>FR - A - 2 023 741</u> (EPROVA AG) * "Revendications" * --	1	
P	<u>EP - A - 0 007 477</u> (DAINIPPON PHARM.) * "Revendications" *	1-5	L: citation for other reasons
The present search report has been drawn up for all claims			&: member of the same patent family, corresponding document
Place of search		Date of completion of the search	Examiner
The Hague		09-03-1981	BRIGHTENTI